PHARMACOLOGY MATERIA MEDICA
AND THERAPEUTICS.

By
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PHARMACOLOGY
MATERIA MEDICA AND THERAPEUTICS

BY
BIRENDRA NATH GHOSH
F.R.F.P.S. (Glas.), F.R.S. (Edin.)
HONORARY FELLOW, STATE MEDICAL FACULTY OF WEST BENGAL
PROFESSOR OF PHARMACOLOGY, R. G. KAR MEDICAL COLLEGE, CALCUTTA ;
AUTHOR OF A TREATISE ON HYGIENE AND PUBLIC HEALTH

NINETEENTH EDITION

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THE USE IN THIS BOOK OF CERTAIN PORTIONS OF THE TEXT OF THE BRITISH PHARMACOPOEIA 1948 IS BY VIRTUE OF PERMISSION RECEIVED FROM THE GENERAL COUNCIL OF MEDICAL EDUCATION AND REGISTRATION OF THE UNITED KINGDOM

PREFACE TO THE NINETEENTH EDITION

THE demand for a new edition of this book so soon after the publication of the last edition in 1949 is gratifying to the author. But the progress whch has been made in pharmacology within recent years is so diverse and widespread that a book becomes almost out-of-date by the time it leaves the press. It has, therefore, been found necessary not only to revise the whole text and delete many old and obsolete matters but to incorporate all the latest advances, some of which have revolutionised treatment of certain diseases at one time considered almost incurable. Moreover, the publication of the Addendum 1951 to the British Pharmacopoeia 1948, necessitated incorporation of all the new additions including the different preparations of Human Blood.

Of the newly introduced monographs are antabuse in chronic alcoholism ; sympathomimetic drugs, e.g. noradrenaline, isoprenaline and dexedrine ; parasympathomimetics like methacholine chloride and meprochol (esmodil) ; syntropan, trasentin, amethone, novatropine, benzhexol (artane) and diethazine hydrochloride (diparcol) as spasmolytics ; tolazoline (priscol) as sympatholytic ; thialbarbitone (kemithal) and quinalbarbitone sodium (seconal sodium) as hypnotics and basal narcotics ; octyl nitrite as a vasodilator ; and dextran as plasma substitute.

Much work has recently been done on anticonvulsant and antihistaminic drugs to justify their inclusion. They are : troxidone (tridione), methoin (mesontoin) and mephenesin (myanesin) as anticonvulsants ; and mepyramine maleate (neoantergan), promethazine hydrochloride (phenergan), antazoline (antistin), phenindamine (thephorin), tripelennamine (pyribenzamine) and chlorcyclizine (histantin) as antihistaminic agents.

Further additions are adrenocorticotrophic hormone (ACTH) and cortisone in the treatment of rheumatoid arthritis ; phenylhydrazine hydrochloride, folic acid antagonists (aminopterin) and mustine (nitrogen mustard) for treatment of leukaemia and other blood diseases. Streptomycin, para-aminosalicylic acid and thiacetazone have been found to be of value in tuberculosis and these have received proper attention. Other additions are vitamin B_{12}, aureomycin and terramycin.

Attention has been drawn to the modern conception of the development of malaria parasites and the comparative value of different antimalarial drugs as a suppressive, curative and prophylactic agents has been discussed.

Because of the increasing application not only as a therapeutic agent in certain malignant diseases but also for investigation as "tracer" substance, a short description of Radioactive Isotopes has been given to enable the student to have some idea regarding these substances.

In this work of revision I have consulted most of the standard works and I gratefully acknowledge the valuable help I received from the British Pharmaceutical Codex 1949 ; The Background of Therapeutics by Professor J. H. Burn ; Pharmacology by J. H. Gaddum ; Pharmacology and Therapeutics by Grollman ; Pharmacologic Principles of Medical Practice by Krantz and Carr ; and Recent Advances in Pharmacology by Robson and Keele.

Finally, I wish to record my appreciation of the help I received from Dr. Nihar Kumar Bhattacharya, B.SC., M.B., Lecturer in Pharmacology in my Department and Dr. M. N. Ghosh, M.B. B.S., Assistant Pharmacologist, Central Drugs Laboratory, Government of India, for their help in not only going through the proof but also for many suggestions.

DEPARTMENT OF PHARMACOLOGY
R. G. KAR MEDICAL COLLEGE
APRIL, 1952

B. N. GHOSH

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PHARMACOLOGY MATERIA MEDICA AND THERAPEUTICS

PART I

MATERIA MEDICA PROPER

MATERIA MEDICA, in its widest sense, means the description of *materials* or *agents* employed in the treatment of disease. But properly speaking, it includes the following branches :—

1. **Materia Medica proper** is the science which treats of the natural history, as well as the physical and chemical characters, of drugs. The term **Pharmacognosy** is used as a synonym to Materia Medica proper.

2. **Pharmacy** is the science and art of preparing and combining drugs, so as to make them fit for administration. It can be divided again as follows :—

(*a*) **Extemporaneous Pharmacy** is the making up or the compounding of formulae or prescriptions of medical practitioners. **Dispensing** refers to the mode of putting up, labelling, and despatching.

(*b*) **Official Pharmacy** consists in the preparation of drugs and formulae according to such processes as are recognised by, or prescribed in, an official pharmacopoeia. The **British Pharmacopoeia** is the official pharmacopoeia of the British Empire.

3. **Pharmacology** is the science which describes the action of drugs on the general system, or on the individual parts of the body, in health. It has been the custom of late to use the term Pharmacology in the same wide sense as Materia Medica was formerly used. **Pharmacodynamics** is but another name for Pharmacology.

Toxicology or the toxic action of drugs comes under Pharmacology. It treats of the actions of drugs when given in doses large enough to endanger life.

4. **Therapeutics** relates to the remedial measures employed in the treatment of disease. It may be either **empirical or rational.**

(*a*) **Empirical Therapeutics** means the treatment of disease from experience only, and conforms to no pharmacological law yet known. In empirical treatment no explanation can be given for the success or otherwise of the use of a particular drug for a particular disease. We merely prescribe a certain drug because it has been found successful in a certain disease. A familiar example is the use of

colchicum in gout. With our improved knowledge on the action of drugs and the pathology of the diseases, we can now explain the actions of many drugs that were used empirically before. Thus, we can explain the action of mercury in syphilis which was formerly used purely empirically.

(*b*) **Rational Therapeutics.**—By rational treatment we mean a mode of treatment suggested by our knowledge of the chemistry, physiology, and pharmacology of a given drug. Thus, when we prescribe $\frac{1}{100}$ gr. of atropine sulphate to check excessive perspiration we can explain (*see* Belladonna) how the perspiration is controlled. The uses of chloral hydrate for checking tetanic convulsions, and of digitalis for the cure of cardiac dropsies, are other instances of rational therapeutics.

Accessory Therapeutics.—By accessory therapeutics is meant the treatment of disease, not by administration of drugs, but by other methods ; such as, change of climate, regulation of food, clothing, exercise, baths, massage, and the like.

DRUGS

By "crude drugs" are meant the commercial forms of the animal or vegetable drugs as are brought to the market and utilised for the preparation of different medicinal products. Their value depends upon the presence of more or less definite chemical bodies known as "active constituents." These constituents are found in different parts of the plant, so that that particular part is used as the crude drug. Sometimes, however, they are found in all parts of the plant. In other instances no part of the plant is used as crude drug ; for instance aloe, where the juice of the leaves contains the active constituent and forms the crude drug.

A. **Source.**—Drugs may be divided. according to their source, into the following groups :—

1. *Inorganic.*—This includes metals, salts, mineral acids, non-metals, like sulphur, etc.

2. *Organic.*—(*a*) From the *vegetable kingdom*, these form a large class. They are derived from roots, leaves, bark, wood, flowers, seeds, and the juice or exudates. (*b*) From the *animal kingdom*, these include cantharidin, lard, pepsin, different gland extracts, hormones, etc.

3. *Synthetic.*—As chloroform, chloral hydrate, ether, amyl nitrite, sulphanilamide, paludrine, mepacrine, etc. Some of these drugs are gradually replacing organic ones ; thus the synthetic salicylic acid is being used for the natural salicylic acid derived from the oil of wintergreen.

B. **Habitat.**—By habitat is meant the natural abode or locality of a plant or animal from which a drug is obtained.

C. **Collection.**—The medicinal activity of a drug depends greatly upon the habitat and the season of the year when it is gathered. Thus, rhubarb is useless until it is six years old. China and Turkey rhubarb are richer than those grown in India. The old cinchona bark is richer in quinine than the new.

COMPOSITION OF DRUGS

Inorganic drugs have a definite composition, which is well expressed by their names and chemical formulae. The composition of

organic drugs on the other hand is always complex and is ascertained after considerable analytical labour. They consist chiefly of acids, bases, salts, albuminous substances, alkaloids, balsams, cellulose, colouring matters, extractive matters, ferments, glycosides, gums, gum-resins, neutral principles, fixed and volatile-oils, oleo-resins, starch, sugar, etc. Some of them require a brief explanation.

Acids are salts of hydrogen. Numerous organic acids are found in plants, either in combination with inorganic bases such as potassium or calcium, or in a free state. Acids and their salts are of great pharmacological interest. Citric acid, tartaric acid, benzoic acid, and mineral acids are some of the acids of the B. P.

Bases are substances which react with acids and form salts. They are of two kinds :—(*a*) *Elementary*, to which metals belong. (*b*) *Compound*, such as ammonium and the alkaloids.

Salts are compounds of acids and bases.

Alkaloids are active nitrogenous principles formed for the most parts in the tissues of plants and animals. They form a prominent group because of their important pharmacological properties. They are organic substances containing nitrogen as their basic character. They are alkaline in reaction and combine with acids to form salts without elimination of hydrogen. A few, coniine, pilocarpine, lobeline, nicotine, contain carbon, hydrogen and nitrogen, and are, as a rule, liquid and volatile. The majority however contain oxygen in addition and are solid and non-volatile.

Pure alkaloids are almost insoluble in water, less soluble in alcohol, but soluble in ether, chloroform and oils. Salts are soluble in water and alcohol, and insoluble in chloroform and ether. They are intensely bitter.

Chemical composition.—The majority of the alkaloids have a complex chemical constitution, and while the structure of some are still obscure, a fair number of them are derived from, (1) *Pyridine*, *e. g.* nicotine, coniine; (2) *Quinoline*, *e. g.* quinine, cinchonine, quinidine, etc. ; (3) *Iso-quinoline*, *e.g.* papaverine, cotarnine, narcotine, hydrastine ; (4) *Phenanthrene*, *e.g.* morphine, codeine, thebaine ; (5) *Pyrrolidine*, *e.g.* cocaine, atropine.

It should be noted that the names of alkaloids in Latin terminate in *ina*, and in English *ine*. As *Atropina* (Latin), *Atropine* (English).

Vegetable alkaloids occur in almost all parts, but are most abundant in the seeds and roots especially of dicotyledonous plants. A few are found in lower plants, *e.g.* *muscarine* and *ergotoxine*. *Bases* found in the animal kingdom are commonly known as leukomains and ptomains. The former are produced by the body cells and are products of metabolism, *e. g.* *adrenaline*, while the latter result from microbic decomposition of dead material, specially the amino-acids. These *bases* are known as amines, and are derived from ammonia by replacing H by alkyl groups.

Some plants contain many alkaloids, *e.g.* cinchona, in others one alkaloid is found in one part of the plant and another in a different part of the same plant.

Alkaloids are also prepared artificially, *e. g.* theophylline, suprarenine. Other artificial alkaloids are apomorphine prepared from morphine ; homatropine, etc.

Incompatibles.—(*a*) *Alkalies*, which precipitate the less soluble pure alkaloid.

(*b*) *Tannin*, forming insoluble tannates.

(*c*) *Iodides* and *bromides*, forming insoluble iodides or bromides, or double salts.

(*d*) *Mercuric chloride*, forming insoluble double salt.

Neutral principles are indifferent crystalline proximate principles which are neutral. They resemble alkaloids in action. The most important are the *glycosides*. Other neutral principles of value are

aloin, santonin, picrotoxin, quassin, etc. Many of them have a bitter taste, as quassin and are called "*amroids or bitter principles.*"

Note.—Whereas the names of all alkaloids end in "*ine*", those of glycosides and neutral principles end in "*in*".

Glycosides are colourless crystalline solids which, under the influence of certain bodies, decompose and yield a reducing sugar and a non-sugar component called *aglucone.* They are found in plants and liberate sugar with acids and certain ferments. They are neutral or weakly acid, and contain carbon, hydrogen and oxygen, a few have nitrogen in addition, and one or two, sulphur. They differ greatly in their solubility in water and alcohol, being mostly insoluble in ether. Some are powerful poisons while others are almost inert. Most of these are laevorotatory and have slightly bitter taste. Salicin, jalapin, digitalin, digitoxin, senegin, strophanthin, glycyrrhizin are some of the glycosides. The term *glucoside* is applied only to those glycosides in which the sugar component is glucose.

Tannins are substances found in many plants specially in the leaves and bark. They are non-nitrogenous. Some are glycosides and form a group of phenol derivatives. They are soluble in alcohol and water, have an astringent taste and give a bluish or greenish colour with iron salts. They are precipitated by heavy metals, albumin and alkaloids. All vegetable astringents contain tannin.

Saponins are non-nitrogenous substances generally glycosides, which emulsify oils and lake red blood-cells. On hydrolysis they yield sugar and a non-sugar component—*sapogenin.* They are neutral in reaction and form froth when mixed with water. The toxic ones are known as sapotoxins. Saponin is found in Senega and Quillaia.

Enzymes or Ferments.—These are a class of unstable bodies, which produce chemical changes without apparently entering into the reaction or forming a part of the end products. They are destroyed at a temperature of 60° C. Examples of ferments are lactase, which converts lactose into glucose and galactose; myrosin which converts sinigrin of mustard seed into allyl-isothiocyanate; pepsin, etc.

Hormones are certain specialised substances having specific actions and are of extreme potency manufactured in specialised cells, notably those of the endocrine glands. Adrenaline, insulin, etc., are some of the hormones extensively used.

Oils of different kinds are used in medicine for a variety of purposes. They are fixed, and volatile.

A. **Fixed Oils** and **Fats** are mixtures of olein (liquid), palmitin (semisolid), and stearin (solid), with a small amount of other bodies in addition. They are found mostly in seeds, occurring within the cells as drops or crystals. They are insoluble in water, sparingly soluble in alcohol, freely in ether, chloroform, benzol, carbon disulphide and turpentine. With alkalies they form soap and glycerin, *e.g.* castile soap, which is made by the action of sodium hydroxide on olive oil, which is practically pure olein, thus :—

$$C_3H_5(C_{18}H_{33}O_2)_3+3NaOH=C_3H_5(OH)_3+3NaC_{18}H_{33}O_2.$$

Oleate of Glyceryl or Olein (Vegetable Oil)	(Caustic Soda)	Hydrate of Glyceryl (Glycerin)	Oleate of Sodium (Hard Soap)

Fats are fixed oils which remain solid at ordinary temperature, but differ from oils in the relative proportion of these basal ingredients, the fats having more of the stearin and palmitin, making them solid or semisolid, and the oils more of the liquid olein.

Characters of fixed oils :—

(*a*) They are non-volatile, and so leave a permanent grease spot on paper;

(*b*) they cannot be distilled ;
(*c*) they decompose under the influence of heat and become rancid ;
(*d*) they are almost bland non-irritating substances (except croton oil) with nutrient and emollient properties ; and
(*e*) they form soaps with alkalies.

A few of the fats and oils are of animal origin, *e.g.* butter, lard, suet and cod-liver oil, but the majority are of vegetable origin as almond, linseed, olive and castor oils, and cocoa butter.

Castor oil and croton oil differ from the others in being soluble in alcohol and in possessing cathartic properties.

The *mineral oils* do not belong to this class of organic drugs. They are petroleum products, being mixtures of hydrocarbons, and do not become rancid.

Waxes are of firmer consistence than the fats, have a higher melting point and cannot be saponified by boiling with an alkali.

B. **Volatile Oils.**—As plants often owe their characteristic odour to these oils they are often spoken of as *essential oils*. They contain a large number of preparations of diverse character and action. They are obtained by a process of distillation, except lemon oil, which is obtained by expression. They are found chiefly in the fruits and flowering parts of plants, or in the seeds and leaves. Owing to their strong characteristic odours they are largely used in perfumery, and to cover the taste and smell of nauseous drugs. As a rule they are clear, colourless liquids ; some like cajuput and cubebs have peculiar greenish colour ; cade, dark reddish-brown ; and cinnamon oil, yellow and when old becomes reddish-brown. The commonest constituents are terpenes, sesquiterpenes and a few diterpenes. Terpenes are hydrocarbons of the aromatic series. In addition, they contain oxidised aromatic substances, as phenols and their derivatives, aromatic alcohols of the benzene series, and their corresponding aldehydes and ketones, aromatic alcohols of the camphor series, and sesquiterpene alcohol.

(*a*) They are volatile and can be distilled, and do not leave a permanent grease spot on paper.

(*b*) They do not form soaps with alkalies as they do not contain any fatty acid.

(*c*) They do not become rancid, but tend to resinify on exposure to light and air ; and

(*d*) They are sufficiently soluble in water to impart to it their taste and odour.

Some of the volatile oils which are non-existent in the living plants are formed either by destructive distillation, or by the action of ferments on glycosides in the presence of water. The former are spoken as **Empyreumatic Oils.**

Bastedo has conveniently grouped the volatile oils as follows :—

A. Existing in plant as such.	1. Terpenes, $CxHx$ (oils of turpentine, juniper, etc.). 2. Terpenes + stearoptenes (oils of lemon, peppermint, etc.).
B. Not existing in plant as such, but developed from plant constituents.	3. From enzyme action (oil of mustard). 4. Empyreumatic oils (oil of cade, oil of tar, creosote).

In group 2 we have the mixture of terpenes holding in solution oxygenated bodies of variable chemical nature. The terpene portion is known as *eleoptene*, the oxygenated portion as *stearoptene*. This stearoptene can be separated from the eleoptene by cold or fractional distillation, and is usually solid. They are therefore oxidised hydrocarbons of a crystalline nature, or solid volatile oils.

The best known examples of stearoptenes are camphor, menthol and thymol.

Lipoids, Lipins, Lipides.—These are a group of substances resembling fats in their solubility in ether, alcohol, etc. They are widely distributed in the animal tissues, chiefly nervous tissues. Lecithin and cholesterol are of interest to us.

Gums are colloidal carbohydrates which swelling or dissolving in water form viscid adhesive fluids known as *mucilage*. They are exudations from the stems, or branches, or both, of plants, and are composed of

(1) *Arabin*, soluble in water; as gum arabic.
(2) *Bassorin*, partially soluble in water; as tragacanth.
(3) *Cerasin*, or insoluble gum.

Pectin or vegetable jelly occur in some medicinal plants and is allied to gum.

Resins are solid, brittle, non-volatile complex substances derived from the oxidation of volatile oils. They are soluble in alkalies forming resin soaps, and in alcohol, but insoluble in water. The resins of the B. P. are colophony, scammony, and podophyllin. When they are found dissolved in volatile oils they are known as **oleoresins,** *e.g.* copaiba, canada turpentine. Sometimes they are found in combination with gums and volatile oils, and are then known as **gum-resins.** They form emulsions when mixed with water. Asafetida is a gum-resin.

Balsams.—These are oleo-resins or resins containing either benzoic or cinnamic acid or both. Benzoin, balsam of Peru and tolu, prepared storax, are the balsams of the B. P. Copaiba and Canada balsam do not come under this group, though they are named balsams.

IMPURITIES OF DRUGS

Impurities in drugs may arise from various causes, the following are the common ones :—

1. **Imperfect Selection.**—This is due to the ignorance of collectors of crude vegetable drugs, who are imperfectly acquainted with their botanical characters and therefore fail to distinguish them from allied species; hence the substitution of an inferior or allied article for the genuine one.

2. **Imperfect Preservation** is one of the causes of deterioration of many drugs. Several drugs are materially affected by light and air, others by the lapse of time. Deliquescent salts and scale iron preparations quickly undergo physical change unless they are kept in carefully stoppered bottles. Syrupus Ferri Iodidi and Easton's Syrup are decomposed by light. Ergot, unless carefully dried and packed in an air-tight receptacle, soon becomes mouldy and loses strength. All extracts deteriorate unless put securely in sealed pots.

3. **Imperfect Preparation.**—Impurities are of two kinds, (*a*) those which exist in the crude drug; (*b*) those which arise as by-products during the process of manufacture. They can be avoided only by scrupulous care on the part of the manufacturing pharmacists.

4. **Adulteration** is the intentional and fraudulent admixture of foreign substances with a drug. All highly priced drugs are liable to adulteration.

THE BRITISH PHARMACOPOEIA AND PHARMACEUTICAL PROCESSES

By a Pharmacopoeia is meant a book published under the authority of a recognised body, generally constituted by law, for the purpose of securing uniformity of composition and strength of medicines

used in the treatment of disease. The General Medical Council of the United Kingdom, authorised by the Medical Act of 1858, issues and revises from time to time the British Pharmacopoeia. The first B.P. was published in 1864, and the last in 1948. Other countries, as the United States, Germany, France, etc., also publish their own Pharmacopoeias. Even hospitals have their own special pharmacopoeias for speedy dispensing. Although the B. P. is the legal standard, no medical man is bound to follow it. Drugs and preparations contained in the British Pharmacopoeia are known as *Official*.

In the year 1946 Government of India published what is called an Indian Pharmacopoeial List which includes vegetable drugs which grow or can be made to grow in India and other chemical and synthetic compounds which are prepared in India. This will be referred to as I.P.L.

The Council of the Pharmaceutical Society of Great Britain periodically publish a book called "The British Pharmaceutical Codex" which contains not only all the drugs and preparations of the British Pharmacopoeia but also many other preparations not contained in it. The abbreviation of the British Pharmaceutical Codex is B.P.C.

The following pharmaceutical processes are generally used :—

Adsorption is the phenomenon of surface condensation. No chemical reaction takes place but the substance (which may be a dye, toxin, gases, etc.) coming in contact with the surface of the adsorbent gets concentrated or fixed, and greater the surface more is the adsorption. It plays an important part in pharmacy. Thus animal charcoal is used to decolourise solutions when the colouring matter is adsorbed on the surface of the charcoal.

Bruising or Contusion is the process by which tough, hard and woody, soft, elastic and juicy substances are smashed or broken up in a roller-mill, or disintegrator, or on a small scale, in an iron mortar, so as to reduce them to a form suitable for being acted upon by a solvent, either by maceration, infusion, or decoction.

Calcination or **Incineration** is the operation by which drugs are exposed to a high temperature in order that watery and volatile matter may be driven off. This is best effected by putting the drugs in a crucible over a furnace.

Crystallization is the process by which substances are made to assume the form of crystals.

Decoction is the process of boiling in water coarsely comminuted vegetable drugs for a definite period, and differs from infusion where the drug is only soaked in either cold or boiling water.

Decolouration is the process by which we remove the colouring matters from alkaloidal substances, such as atropine, morphine, etc. This is effected by treating their solutions or mixtures with dried and purified animal charcoal, and subsequent filtration.

Despumation is the process by which an organic fluid is boiled until the impurities rise to the surface as scum, which is then removed by skimming or straining. Syrups made by this process keep longer.

Dialysis is the process of separating crystalloids from colloids by passing them through an animal membrane.

Digestion is a prolonged maceration at a temperature higher than that of the air.

Elutriation is the process by which a substance is pulverised and mixed with water, the coarser grains falling down to the bottom, while the lighter and finer ones are poured off with the water into another vessel, where deposition takes place slowly.

Expression is the process by which we press out juices and oils from vegetable substances, as in the preparation of succi, or squeeze out the liquid from the marc as in the preparation of tinctures. For this process suitable presses are required.

Fusion, Liquefaction or **Melting** is the process by which we melt or liquefy any solid body by heat. This is effected by putting it into a suitable vessel or crucible over a heated furnace, or on a water, steam or sand bath. We employ this process in the preparation of plasters, ointments, suppositories, caustic sticks, etc.

Granulation is the process by which coarsely, crystalline salt is converted into a granular powder by dissolving the former in water, and evaporating the solution to dryness with continuous stirring. Carbonate and citrate of potassium are made in this way.

Levigation is the pulverisation of a solid in the presence of water, or any other liquid which does not dissolve it ; the finely comminuted particles being gathered with the washings and allowed to deposit slowly, whilst the coarser particles are again ground with the water or liquid, and so on, until the whole of the solid is reduced to a condition of fine powder.

Lixiviation means the separation of a soluble salt, from a mixed or compound solid, by dissolving the latter in water, decanting the supernatant liquid into another vessel, and evaporating it to dryness, leaving the insoluble residue behind. The solution is called a "*Lye*".

Maceration is the process of steeping a substance in alcohol, or some similar menstruum without the application of heat, in order to dissolve out its soluble matters. The insoluble residue is called the "*marc.*"

Percolation is the process of extracting soluble matters by filtration of a liquid menstruum through a porous column of powdered material. A special apparatus, called a percolator, is required.

Scaling is the process by which the scale preparations of drugs are made. It consists in spreading out in a thin layer, the concentrated solution of a drug on a glass, and allowing it to dry. The dried film is then separated and broken up. The scale iron preparations are made by this process.

Sifting is the method by which we separate finer powders from coarser ones by means of a sieve, which is made of either wire, horse-hair or muslin, of varying degrees of closeness. The B.P. directs a drug in No. 44, 60, 85, or 120 powder, and thereby means a degree of disintegration, as represented by the number of parallel wires in either transverse direction contained within the linear inch of a sieve.

When the soft pulp of fruits like figs, baels, prunes, or tamarinds is required to be sifted, the operation is called "**pulping**" which requires a great force in squeezing the pulp through the sieve.

Solution implies dissolving a solid into a liquid whereby the molecules of the solid disperse themselves into the liquid in such a way that no solid portion can be distinguished. This is *simple solution*, the change being physical. It is generally effected by putting the solvent in contact with the substance to be dissolved, and is often hastened by heat. The liquid which dissolves the solid is called the *solvent*. Ordinarily. as happens in simple solution, a solvent is capable of dissolving only a limited amount of a given solid, but when a solvent dissolves as much of the solid as it can contain, the solution is called a *saturated solution*. If saturated solution is made at a high temperature, the solid so dissolved in excess of saturation, may under certain conditions remain in solution at a lower temperature, when it is called *supersaturated solution*. But the excess of solid so dissolved separates and crystallizes out on cooling.

Sublimation is the operation by which a solid is first vaporised by heat, and then the vapour is condensed as a deposit on the surface of another vessel, either *en masse*, in which case it is called a **sublimate**, as corrosive sublimate, or in a small feathery pulverulent state, known as flowers. as flowers of sulphur.

WEIGHTS AND MEASURES OF THE BRITISH PHARMACOPOEIA

METRIC SYSTEM

Measures of Mass (Weights)

1 Kilogram (kg. or kilog.) is the mass of International Prototype Kilogram

1 Gramme (g.)	=	the 1000th part of 1 kilogram
1 Milligram (mg.)	=	the 1000th part of 1 gramme
1 Microgram (γ or μg.)	=	the 1000th part of 1 milligram

For the purpose of writing prescriptions, in order to avoid the possibility of confusion between 'gramme' and 'grain', the symbol 'G' should be used as the contraction for 'gramme'.

Measures of Capacity (Volumes)

1 Litre (lit.) is the volume occupied by the mass of 1 kilogram of water at the temperature of its maximum density.

1 Millilitre (ml.)=the 1000th part of 1 litre.

1 litre measures about 1000.027 cubic centimetres.

Measures of Length

1 Metre (m.) is the length of International Prototype Metre at 0°.

1 Centimetre (cm.)	=	the 100th part of 1 metre
1 Millimetre (mm.)	=	the 1000th part of 1 metre
1 Micron (μ)	=	the 1000th part of 1 millimetre
1 Millimicron (mμ)	=	the 1000th part of 1 micron

IMPERIAL SYSTEM

Measures of Mass (Weights)

1 Pound (Avoir.) (lb.) is the Standard Pound as defined in the Weights and Measures Act, 1878, Section 13.

1 Ounce (Avoir.) (oz.)	=	the 16th part of 1 pound = 437.5 grains
1 Grain (gr.)	=	the 7000th part of 1 pound

Measures of Capacity (Volumes)

1 Pint (pt.) is the Imperial Standard Pint as defined in the Weights and Measures Act, 1878, Section 15.

1 Fluid Ounce (fl. oz.)	=	the 20th part of 1 pint=8 fl. dr.
1 Fluid Drachm (fl. dr.)	=	the 8th part of 1 fluid ounce=60 min.
1 Minim (min.)	=	the 60th part of 1 fluid drachm.

Relation of Capacity to Weight (Imperial)

1 Minim	=	the volume at 16.7° C. (62° F.) of 0.91146 gr. of water
1 Fluid Drachm	=	the volume at 16.7° C. (62° F.) of 54.688 gr. of water
1 Fluid Ounce	=	the volume at 16.7° C. (62° F.) of 1 oz. or 437.50 gr. of water
109.71* Minims	=	the volume at 16.7° C. (62° F.) of 100 gr. of water.

In the B.P. "per cent." is used to mean the following :—

Per cent. w/w=weight in weight.
Per cent. w/v=weight in volume.
Per cent. v/v=volume in volume.

* Taken as 110 minims throughout the Pharmacopoeia

Relations of Metric and Imperial Measures

Mass

1 Kilogram (kg. or kilog.)	=	15,432 grains, or 35.274 ounces or 2.2046 pounds
1 Gramme (g.)	=	15.432 grains
1 Milligram (mg.)	=	0.015432 grain
1 Pound (Avoir.) (lb.)	=	453.59 grammes
1 Ounce (Avoir.) (oz.)	=	28.350 grammes
1 Grain (gr.)	=	0.064800 gramme

Capacity

1 Litre (lit.)	=	1.7598 pints, or 35.196 fluid ounces
1 Millilitre or Mil (ml.)	=	16.894 minims
1 Pint (pt.)	=	568.25 mils., or 0.56825 litre
1 Fluid Ounce (fl. oz.)	=	28.412 mils
1 Fluid Drachm (fl. dr.)	=	3.5515 mils
1 Minim (min.)	=	0.059192 mil.

Length

1 Metre (m.)	=	39.370 inches
1 Centimetre (cm.)	=	0.39370 inch
1 Millimetre (mm.)	=	0.039370 inch
1 Micron (μ)	=	0.000039370 inch
1 Inch (in.)	=	25.400 millimetres

TABLE OF APPROXIMATE EQUIVALANCES ADOPTED IN STATING DOSES (IMPERIAL AND METRIC) IN THE BRITISH PHARMACOPOEIA

Millilitres Grammes	Minims Grains	Millilitres Grammes	Minims Grains
10	150	0.8	12
8	120	0.6	10
6	90	0.5	8
5	75	0.4	6
4	60	0.3	5
3	45	0.25	4
2.6	40	0.2	3
2	30	0.15	2½
1.6	25	0.12	2
1.3	20	0.1	1½
1	15		

Milligrams	Grain	Milligrams	Grain
80	1¼	2.5	1/24
60	1	2	1/30
50	3/4	1.5	1/40
40	3/5	1.2	1/50
30	1/2	1	1/60
25	2/5	0.8	1/80
20	1/3	0.6	1/100
16	1/4	0.5	1/120
12	1/5	0.4	1/160
10	1/6	0.3	1/200
8	1/8	0.25	1/240
6	1/10	0.2	1/320
5	1/12	0.15	1/400
4	1/16	0.12	1/500
3	1/20		

STANDARDIZATION OF DRUGS AND BIOLOGICAL ASSAY

Standardization is the method adopted to obtain a definite uniformity in the strength of certain preparations containing active or alkaloidal principles, such as the extract of nux vomica, tincture of strophanthus, etc. This may be accomplished by chemical or biological methods, generally expressed as pharmaceutical assaying. This secures a means of measuring therapeutic activity and makes it possible to furnish uniform preparations. Biological methods are used for the assay of certain substances and preparations, the purity or potency of which cannot be adequately determined by chemical or physical means. Chemical methods are used for all other preparations. The essential conditions of all biological assays are :—(i) the biological effect produced by the sample must be compared with that of the Standard Preparation; (ii) the tests with the sample and the Standard Preparation should be carried out simultaneously; and (iii) the test should be carried out under strictly comparable conditions.

The pharmacopoeia gives details of the methods to be followed in each case, and it should be consulted. The following are the principle methods.

1. *Toxic Method.*—Guinea-pigs, frogs, cats or other animals are generally selected for the test, and the value of the drug or preparation is calculated on the amount required to cause the death of the animal.

2. The amount required to produce certain definite effects on the animals, *e. g.* cock's comb method for ergot.

3. The amount required to produce a definite effect on an isolated organ, *e.g.* effect of pituitary extract on isolated uterus.

4. The amount required to clear the peripheral blood of mice infected with trypanosomes within 24 hours.

According to the British Pharmacopoeia the following preparations are biologically assayed :—

Neoarsphenamine and **Sulpharsphenamine.**—These must comply with the test for absence of undue toxicity and for therapeutic potency.

Neoarsphenamine.—(a) *Absence of undue toxicity.*—Two groups of mice, 20 in each group, the fasting weights not differing by more than 3 grm. are used in the test. One group is injected with the sample and the other with the Standard Preparation. The dose of the Standard Preparation is so selected that it causes approximately 50 p. c. mortality; the dose of the sample used is 20 p. c. less than that of the standard. If the mortality with the sample is not greater than that with the standard, the sample passes the test. A 2.0 p. c. solution of the sample and the standard is used for the test and the observation for mortality is made during the 3 days following injection.

(b) *Therapeutic potency.*—This is tested against *Trypanosoma equiperdum* infection of white mice. A dose of the sample 20 p. c less than that of the Standard Preparation is used. The dose of the standard is so selected that it causes disappearance of trypanosomes from approximately 50 p. c. of an adequately large number of mice injected. If the total number of mice, out of the 20 used, cleared by the sample being tested is equal to or greater than that cleared by the Standard Preparation, the sample passes the test. A 0.1 p. c. solution of the sample and the standard is used for the test and the observation is made during the 1st and 3rd days following the injection.

Sulpharsphenamine is injected subcutaneously. For therapeutic potency test a 0.2 p. c. solution is used and the observation is made on the 3rd and 4th day following the injection. In addition sul-

pharsphenamine must pass the test for local irritant effect in white rats, which is tested by giving subcutaneous injection of a 10.0 p. c. solution in a dose of 0.35 mg. per grm. of body weight. This should not cause oedema or local necrosis at the site of injection or death of more than 1 out of 10 or 2 out of 15 rats injected.

Digitalis.—The International Unit is the activity contained in 0.08 grm. of the Standard digitalis powder. (1) The *frog* test consists of making injections of suitable dilutions of the extract of Standard Preparation and of the sample into similar groups of frogs and determining the amount of extract in mils required to produce death by systolic standstill of the ventricle per 100 grm. frog within 24 hours. The potency is calculated by comparing with that of the standard the percentage mortality amongst the frogs.

(2) *Cat or guinea-pig test* is done by injecting into a vein at a slow uniform rate extract of special strength into anaesthetised animals and determining the amount required to arrest the heart. The potency is determined by dividing the average lethal dose of the Standard Preparation by the dose required of the sample preparation.

Strophanthus and **Tincture of Strophanthus** are standardized in the same way.

Insulin.—The Standard Preparation is a quantity of pure dry crystalline insulin hydrochloride, kept at the National Institute for Medical Research, Hampstead, London. The potency of a sample of insulin is estimated by comparing the hypoglycaemic effect it produces with that produced by the Standard Preparation of insulin under the conditions of a suitable method of assay.

Rabbit method.—Healthy rabbits weighing between 1,800 to 2,000 grm. are selected and are deprived of food eighteen hours preceding the assay. The animals are distributed over 4 equal groups at random, each group containing at least 3, but preferably more, rabbits. The initial blood sugar for each rabbit is determined.

Two dilutions of the Standard Preparation, containing 2 units and 1 unit respectively in each ml. are prepared. Each of the rabbits of group 1 receives subcutaneous injection of its Standard Volume of the stronger solution and group two animals receive similar injection of the weaker solution. Similarly groups 3 and 4 animals are injected subcutaneously with the Standard Volume of the two dilutions of the sample, expected to contain 2 units and 1 unit in each ml. respectively. Hourly samples of blood for five hours after injection are withdrawn and the mean blood sugar, expressed as mg. of glucose per 100 ml. in the five samples is determined for each rabbit.

On a second day the test is repeated after preliminary fasting as above, by crossing over the rabbits, those injected with the Standard Preparation previously receiving the sample and vice-versa. On this occasion the animals which received the larger doses before receive the smaller dose.

The potency is determined by comparing the percentage blood sugar reduction produced with the sample with that produced with the Standard Preparation with necessary corrections. Any rabbit which convulses or shows other abnormal symptoms during the test is discarded.

Pituitary (posterior lobe) Extract.—The Standard Preparation is a quantity of dried acetone extracted substance, obtained from the posterior lobe of fresh pituitary bodies of oxen. The Unit is defined as the specific activity (oxytocic, antidiuretic or pressor) corresponding to that yielded by 0.05 mg. of the Standard Preparation, when extracted by the prescribed method.

The potency of a sample may be determined by any of the methods—oxytocic, antidiuretic, or pressor.

Oxytocic activity.—This is tested in isolated virgin guinea-pig uterus, suspended in special oxygenated *saline solution* at a tempera-

ture of 37°C. A dose of the sample of suitable identical dilution as the Standard Preparation, which produces equal submaximal contraction as that with the standard is determined and the potency is calculated in terms of the standard. The activity of the extract is **expressed in Units per ml.**

Antidiuretic activity.—This is tested in 16 white male rats weighing between 120 and 240 grm. divided in 4 equal groups. Each rat receives warm water by stomach tube and immediately injected subcutaneously with the pituitary extract. Two groups are injected with Standard Preparation and two with the sample under test. The groups are crossed over on a different day. The potency of the sample is calculated in terms of the standard from a predetermined **standard curve.**

Pressor activity.—This is tested in spinal cats. Blood pressure rise with different doses of the sample is compared with that produced by a constant dose of the Standard Preparation of suitable identical dilution and the potency is calculated from that.

Old Tuberculin.—The potency is tested by comparing the dose necessary to produce its specific toxicity in guinea-pigs or other animals infected with the *M. tuberculosis*, with the dose of the Standard Preparation of Old Tuberculin, necessary to give the same effects. The inflammatory reaction is produced after 24 hours. A sample of old tuberculin is considered to have passed the test only if no difference in its activity from that of the Standard Preparation **is revealed.**

Diphtheria Antitoxin.—The Standard Preparation is a quantity of dried diphtheria antitoxin ; the Unit is contained in 0.1279 mg. of the Standard Preparation. The potency is determined by comparing the dose necessary to protect guinea-pigs or other suitable animals against the effect of a fixed dose of diphtheria toxin, with the dose of Standard Preparation of diphtheria antitoxin, necessary to give the same protection. For this comparison there are necessary (*a*) the Standard Preparation of Diphtheria Antitoxin, and (*b*) a suitable preparation of diphtheria toxin for use as a test toxin.

Gas-gangrene Antitoxin (perfringens).—Its potency is determined by comparing the dose necessary to protect mice or other suitable animals against the lethal effect of gas-gangrene toxin, with the dose of a Standard Preparation of Gas-gangrene Antitoxin (perfringens), necessary to give the same protection.

The same procedure is followed in determining the potency of Gas-gangrene Antitoxin (oedematiens or vibrion septique). For this purpose there are necessary (*a*) the Standard Preparation of Gas-gangrene Antitoxin (perfringens, oedematiens or vibrion septique) ; and (*b*) a suitable preparation of gas-gangrene toxin of any **of the three varieties for use as a test toxin.**

Tetanus Antitoxin.—The Standard Preparation is a quantity of dried tetanus antitoxin; the Unit is contained in 0.1770 mg. of the Standard Preparation. The potency of a sample is determined by comparing the dose of it, necessary to protect guinea-pigs or mice against the lethal effect of a fixed dose of tetanus toxin, with the dose of the Standard Preparation of Tetanus Antitoxin, necessary to give the same protection. For the comparison of potency there are necessary (a) the Standard Preparation of Tetanus Antitoxin, and (b) a suitable preparation of tetanus toxin for use as a test toxin.

Staphylococcus Antitoxin.—The potency is determined by comparing the dose necessary to neutralise the specific haemolytic, dermo-necrotic or lethal effects of staphylococcus toxin, necessary to give the same protection. For this purpose are necessary, (*a*) the Standard Preparation of Staphylococcus Antitoxin, (*b*) a suitable preparation of staphylococcus toxin for use as a test toxin.

Antirachitic Vitamin D.—The activity of Vitamin D is determined by comparing its antirachtic activity with that of the Stan-

dard Preparation of Great Britain and Northern Ireland, kept in the National Institute of Medical Research and is expressed in Units per gramme.

(*a*) *Curative.*—Young rats of more or less uniform weight are fed for about 3 weeks on a rachitogenic diet and the degree of rickets determined by taking X-ray photographs. The rats are then divided into 4 equal groups; rats in 2 groups receive doses of the Standard Preparation in the ratio of 1 to 2 or 1 to 3, etc. ; rats of the other 2 groups receive doses of the sample in the same ratio as the doses of the standard. The extent of the cure of rickets with the sample and the standard is compared 10 to 14 days after by X-rays or staining of bones.

(*b*) *Prophylactic.*—Young rats divided in 4 equal groups are fed on one of the rachitogenic diets for 4 or 5 weeks. During this time the rats of different groups receive daily doses of the Standard Preparation or of the preparation being tested in ratio 2 to 1. Suitable doses of the Standard Preparation may vary from 0.025 to 0.1 unit. At the end of this period the animals are killed and the ash content of the corresponding bone determined separately for each rat and the average ash content of 4 groups compared.

Vitamin A.—The activity of a preparation of Vitamin A is determined by comparing its activity with that of the Standard Preparation of vitamin A, or with that of a subsidiary laboratory standard, the activity of which is known in terms of the Standard Preparation.

The Unit is defined as the specific activity contained in 0.6 microgram (0.6γ) of the Standard Preparation of β-carotene.

Assay is made by one of the following methods, viz.—

(*a*) By increase in weight in rats which have ceased to grow on a diet deficient in vitamin A.

(*b*) *By Spectrophotometric Method.*—This method measures the amount of a substance having a certain physical property characteristic of vitamin A.

Chorionic Gonadotrophin.—The activity of a preparation containing chorionic gonadotrophin is determined by comparing its gonadotrophic activity with that of the Standard Preparation of Chorionic Gonadotrophin by a suitable biological method. The weight of the ovaries of the immature female rat can be increased by the action of chorionic gonadotrophin from an unstimulated level of about 10 mg. to a maximum of about 40 mg. or more (luteinisation checked by microscopical examination) if very large doses are given. This increase is the basis of the assay.

Rats weighing between 40 and 50 grm. are divided into four equal groups of not less than ten animals in a group. Animals in two groups are injected subcutaneously with two doses of the Standard Preparation (total dose divided into five equal parts and administered daily for five days) which are expected to produce a mean ovary weight of 15 to 20 mgm. and 30 to 35 mgm. respectively (doses being determined by a preliminary pilot assay). Rats in the remaining two groups receive corresponding doses of the preparation under test. Two dose-response curves are constructed and differences between the slopes and differences in mean response to the standard and other preparation are examined.

Serum Gonadotrophin.—The assay method is similar to that of Chorionic Gonadotrophin, but the characteristic action is stimulation of follicular growth as checked by microscopical examination. The increase in weight of ovaries is much more in this case—may be up to 200 mg.

Heparin.—The Standard Preparation is a quantity of the dried sodium salt of heparin, prepared from the crystallised barium salt of ox heparin. The Unit is contained in 0.0077 mg. of the Standard Preparation. The potency of a sample of heparin is determined by comparing the concentration of it, necessary to prevent the clotting

of shed blood, or of a fluid containing some of the substances which take part in the reactions leading to the clotting of shed blood, with the concentration of the Standard Preparation necessary to give the same effect.

For the assay, one of the following may be employed :—(a) the freshly shed blood of the cat or other suitable animal, (b) fowl plasma to which a tissue extract has been added to promote clotting, or (c) the decalcified blood or plasma of various mammalian species used in conjunction with a solution of a calcium salt alone or combined with a tissue extract or a solution of thrombin.

Fifteen tubes of as nearly as possible equal internal diameter, arranged in five groups of three, are filled with 0.1, 0.2 and 0.3 ml. of a dilution of standard (containing 2.5 units per ml.) and four dilution of the sample test (expected strength 2.5, 2.25, 2.0 and 1.75 units per ml.). Solution of each tube is made up to 0.3 ml. by the addition of saline solution. Freshly drawn blood is added (run directly from the carotid artery) to each tube up to 1 ml., mixed and incubated at 37°C. in a water bath for two hours. The degree of clotting in each tube is recorded and compared.

Penicillin.—The Standard Preparation is a quantity of the sodium salt of a pure preparation of penicillin II, or G. The Unit is contained in 0.00065 mg. of the Standard Preparation. The potency of a sample of penicillin is determined by comparing the dose of it which inhibits the growth of a sensitive strain of *staphylococcus* with the dose of a Standard Preparation of penicillin which produces the same degree of inhibition. The methods are—

A. *The Cylinder-Plate Method.*—Petri dishes, or rectangular trays are filled to a depth of 2 to 5 mm. with agar culture medium, which is previously or subsequently inoculated, in as uniform a manner as possible with a suitable culture of *staphylococcus.* Small sterile cylinders, approximately 10 mm. high and having an internal diameter of approximately 5 mm. made of glass, porcelain or aluminium are carefully placed on the surface of the inoculated medium. These are filled with solutions of the Standard Preparation of known concentration and sample under test, presumed to be of the same order of concentration. The plates are incubated at 37°C. for 16 to 24 hours and the diameters of the inhibition zone with different dilutions are measured with the greatest possible accuracy and the potency of the sample calculated in terms of the standard.

B. *The Broth Dilution Method.*—Tubes containing a suitable liquid culture medium are arranged in two series. Different known dilutions of the Standard Preparation of Penicillin are added to one series of tubes and the sample under test diluted identically as the standard are added to the other series. Uniform small inoculum of a suitable strain of *staphylococcus* is added to each tube ; the tubes are incubated at 37°C. for 15 to 18 hours and the inhibition of growth in different tubes compared.

OFFICIAL OR PHARMACOPOEIAL PREPARATIONS

Few drugs can be administered in their natural state. They are either too nauseous, too bulky, or contain some principles which are injurious to life or health. They are, therefore, submitted to certain processes prescribed by the British Pharmacopoeia, in order to render them fit for administration, and also to help their preservation and storing, so as to maintain an uninterrupted supply during all seasons of the year. In the following pages we have given all the official preparations of the B.P. 1948 in a

tabular form, with their composition, strengths, doses, and in some instances, their actions and uses.

Aceta.—These are solutions of drugs in acetic acid, not in Vinegar. There is only one in the B.P.

Acetum Scillae.—Squill bruised 10 grms., acid acetic dilute 100 mils. **Dose.**—10 to 30 ms. or 0.6 to 2 mils.

Acida Diluta.—Diluted Acids are strong acids diluted with distilled water. They are four in number.

Acidum	Preparation.	Dose.	Action and Uses.
Aceticum Dil.	Acetic acid 182 grm., water 818 grm.	..	Refrigerent.
Hydrochloricum Dil.	Hydrochloric acid 274 grm., water, 726 grm.	10 to 120 ms. or 0.6 to 8 mil.	In acid dyspepsia and gastric troubles.
Hypophosphorosum Dil.	Barium hypophosphite and dilute sulphuric acid. 10 p. c. hypophosph. acid.	5 to 15 ms. or 0.3 to 1 mil.	..
Phosphoricum Dil.	Phosphoric acid 112 grm., water 888 grm.	5 to 60 ms. or 0.3 to 4 mil.	Tonic, refrigerent.

Adeps and Adeps Lanae. Lard and Wool Fat. Two preparations, as follows :—

Adeps Benzoinatus.—Lard 1000 gm., powdered benzoin 20 gm. Melt the lard in a water-bath, mix and strain.

Adeps Lanae Hydrosus. *Syn.—Lanolin.*—Wool fat 700 gm. distilled water 300 mils. Mix by trituration in a warm mortar.

Antitoxina.—An **antitoxin** is serum, or a preparation from serum, containing the antitoxic globulins or their derivatives, which have the specific power of neutralising the toxins formed by a micro-organism. There are six in the B.P. *These are all administered by injection.*

Antitoxinum	Composition	Dose
Diphthericum	Contains the antitoxic globulins or their derivatives having specific power of neutralising toxins formed by *Corynebacterium diphtheriae.*	*Prophylactic* : 500 to 2000 Units ; *Therapeutic* : not less than 10,000 Units.
Oedematiens	Contains the antitoxic globulins, or their derivatives, having the specific power of neutralising the toxins formed by *Clostridium oedematiens.*	*Prophylactic* : 10,000 Units ; *Therapeutic* : not less than 30,000 Units.
Oedematiens Co.	Prepared by mixing Gas-gangrene Antitoxin (oedematiens). Gas-gangrene Antitoxin (perfringens), Gas-gangrene Antitoxin (septicum).	*Prophylactic* : Oedematiens and Perfringens, not less than 10,000 Units each ; Septicum not less than 5,000 Units. *Therapeutic* : not less than 30,000 Units for oedematiens and perfringens and not less than 15,000 Units for septicum.
Septicum	Contains the antitoxic globulins or their derivatives having the specific power of neutralising the toxins formed by *Clostridium septicum.*	*Prophylactic* : 5,000 Units *Therapeutic* : not less than 15,000 Units.
Tetanicum	Contains antitoxic globulins or their derivatives, having the specific power of neutralising the toxins formed by *Clostridium tetani.*	*Prophylactic* : not less than 3,000 Units ; *Therapeutic* : not less than 100,000 Units.
Welchicum	Contains the antitoxic globulins or their derivatives, having the specific power of neutralising the toxins formed by *Clostridium perfringens.*	*Prophylactic* : 10,000 Units; *Therapeutic* : not less than 30,000 Units.

Aquae. Waters.—With the exception of distilled water, water for injection and chloroform water, all aquae are weak and simple

solutions of volatile oils obtained as described under aromatic waters. They are six in number.

Aqua	Preparation	Dose	Action
Anethae Conc.	Oil of dill 2 mil., alcohol (90 p.c.) 60 mil., water q. s. to 100 mil.	5 to 15 ms. (0.3 to 1 ml.)	Carminative.
Camphorae	Camphor 1 gm., alcohol (90 p.c.) 2 mil., and distilled water 1000 mil. By solution.	1/2 to 1 oz. (15 to 30 ml.)	Stimulant and antispasmodic. As a vehicle.
Chloroformi	Chloroform 2.5 mil., distilled water to 1000 mil. ; by solution.	1/2 to 1 oz. (15 to 30 ml.)	A flavouring agent.
Cinnamomi Conc.	Cinnamon oil 20, alcohol (90 p.c.) 600, water q.s. 1000.	5 to 15 ms. (0.3 to 1 ml.)	Carminative, flavouring agent.
Destillata	Distilled from natural potable water.	...	A vehicle.
Menthae Pip. Conc.	Peppermint oil 20, alcohol (90 p.c.) 600, water q.s. 1000.	5 to 15 ms. (0.3 to 1 ml.)	An antispasmodic and carminative vehicle.

Aquae Aromaticae.—Aromatic Waters are prepared either by (*a*) *solution*, *i. e.* by shaking the essential oil with five hundred times its volume of distilled water for fifteen minutes and filtering after 12 hours; or by triturating the oil with powdered talc, kieselguhr, or pulped filter paper, and five hundred times its volume of distilled water, and filtering ; or (*b*) by diluting the concentrated water with 39 times its volume of distilled water.

N. B.—Concentrated aromatic waters are weak alcoholic solutions of volatile oils which when diluted with 39 times its volume of distilled water yield a preparation which is approximately equivalent to distilled aromatic water in strength, but contains about 1.5 p.c. v/v of alcohol (90 p.c.).

Aqua Pro Injectione.—Water for Injection.—Distil potable water from a neutral glass or metal still fitted with an efficient device for preventing entrainment. Reject the first portion and collect the remainder in a neutral glass container. Close the container to exclude bacteria and immediately sterilise by *heating in an autoclave.*

Cataplasmata.—Poultices are thick pasty preparations intended for local application, either cold or hot. Only one preparation, viz.—

Cataplasma Kaolini. *Syn.—Kaolin Poultice.*—Heavy Kaolin (finely sifted) 527 grm., boric acid (finely sifted) 45 grm., methyl salicylate 2 mil., oil of peppermint 0.5 mil., thymol 0.5 grm., glycerin 425 grm.

N. B.—Should be kept in a well-closed container.

Collodia.—Collodions are solutions of drugs in collodion, or solution of pyroxylin in ether and alcohol.

Collodium Flexile.—Pyroxylin 2 gm., colophony 3 gm., castor oil 2 gm., alcohol (90 p.c.) 24 mil., ether q.s. to 100 mil. The alcohol (90 p.c.) may be replaced by Industrial Methylated Spirit of the same strength.

Cremors.—Creams are soft or semi-liquid preparations for external application. There are only two in the B.P.

Cremor Penicillini. *Syn.—Penicillin Cream.*—Penicillin (sodium or calcium salt), q.s. ; emulsifying wax, 7 grm. ; hard paraffin, 5 grm. ; liquid paraffin, 41 grm.; chlorocresol, 0.1 grm.; water 47 mil.

Cremor Penicillini Sterilisatus.—Penicillin, q.s.; emulsifying wax, 7 grm.; hard paraffin, 5 grm. ; liquid paraffin 41 grm. ; water 47 mil.

N. B. When any of the cream is prescribed cream with 500 units per grm. should be dispensed.

Elixiria.—Elixirs are weak tinctures of drugs rendered pleasant and agreeable by admixture of sugar and aromatics. Only one in the B.P., viz.—

Elixir Cascarae Sagradae.—Cascara sagrada in coarse powder 1000 grm., liquorice, unpeeled, in coarse powder 125 grm., light magnesium oxide 150 grm., saccharin sodium 1 grm., oil of coriander 0.15 mil., oil of anise 0.2 mil., alcohol (90 p.c.) 125 mil., glycerin 200 mil., distilled water, q.s. to 1000 mil. **Dose.**—2 to 4 mils or 30 to 60 ms.

Emulsio.—Emulsions are suspensions of oily or resinous substances by means of an adhesive substance known as **emulsifier** or **emulgent.** There are four in the B. P.

Emulsio	Composition	Dose
Chloroformi	Chloroform, 50 ; liquid extract of quillaia, 1 ; mucilage of tragacanth, 50; water q.s. 1000.	5 to 30 ms. or 0.3 to 2 mil.
Menthae Pip.	Oil of peppermint, 100; liquid extract of quillaia, 2.5; water q.s. 1000.	5 to 30 ms. or 0.3 to 2 mil.
Olei Morrhuae	Cod-liver oil, 500 mil ; acacia powder, 125 G. ; tragacanth powder, 7 G. ; volatile oil of bitter almond, 1 mil ; saccharin sodium, 0.1 G. ; chloroform, 2 mil ; water q.s. 1000 mil.	120 to 360 ms. or 8 to 24 mil. in divided doses, daily
Paraffini Liq.	Liquid paraffin, 500 mil ; acacia powder, 125 G. ; tragacanth powder, 5 G. ; glycerin, 125 mil ; sodium benzoate, 5 G. ; vanillin, 0.5 G. ; chloroform, 2.5 mil ; water, q.s. 1000 mil.	1/4 to 1 oz. or 8 to 30 mil.

Extracta. **Extracts.**—These are prepared by extracting the active principles either with water, alcohol, or both, or with ether. They contain different active principles in a very concentrated form with very little inert substance. Different methods are used for extraction, viz., *maceration*, *infusion*, *percolation* and *decoction.* According to the consistency of the different extracts they have been divided into, **Dry** or **Solid, Semisolid** or **Soft,** and **Liquid.**

The B. P. directs that the industrial methylated spirit of equivalent strength may be substituted in place of alcohol in the preparation of the different extracts provided no industrial methylated spirit is left in the finished product.

Of the different extracts, Ext. Fellis Bovini, Ext. Hepatis Liq., and Ext. Maltı c. Oleo Morrh., are animal products.

Semisolid or **Soft Extracts** are prepared by dissolving, macerating, infusing or boiling drugs, in cold or hot distilled water, and evaporating the solution, infusion or decoction, as the case may be, to the consistence of a soft extract. They are four in number.

Extractum	Ingredients	Process	Menstruum	Dose
Fellis Bovini	Ox gall	E.	Alcohol	5 to 15 gr. 0.3 to 1 G.
Glycyrrhizae	Dried root	P. & E.	Chloroform water	10 to 30 gr. 0.6 to 2 G.
Malti	Malted grain of Barley	Digestion & E.	Water	60 ms. to 1 oz. 4 to 30 mil.
Malti c. Oleo Morrhuae	Malt extract 9 gm., Cod-liver oil 1 gm. (10 p.c. Cod-liver oil.)		Ext. Malt	60 ms. to 1 oz. 4 to 30 mil.

The strengths of the soft extracts are not adjusted, but since they do not contain any potent principle this is of little consequence.

Liquid Extracts are prepared from drugs with water as the solvent and alcohol is added for their preservation against fermentation and fungoid growth. They are fourteen in number.

E=Evaporation. P=Percolation.

Extractum	Ingredients	Alcohol p.c. in the menstruum	Strength	Dose
Belladonnae Liq.	Belladonna root, alcohol, water.	80	0.75 p.c. alkaloids	..
Cascarae Sagr. Liq.	Cascara powder 1000 grm., alcohol 250 mil., water q.s. to 1000 mil.	90	50 p.c.	30 to 60 ms. 2 to 4 ml.
Colchici Liq.	Colchicum seed 1000 grm., alcohol q.s. 1000 mil.	60	0.3 p.c. colchicine	..
Ergotae Liq.	Ergot 1000 grm., tartaric acid, alcohol, each q.s.	50	0.06 to 0.04 p.c. ergotoxine	10 to 20 ms. 0.6 to 1.2 ml.
Glycyrrhizae Liq.	Liquorice 1000 grm., chloroform water and alcohol q.s.	90	..	30 to 60 ms. 2 to 4 ml.
Hamamelidis Liq.	Hamamelis 1000 grm., alcohol q.s. to 1000 ml.	45	50 p.c.	..
Hepatis Liq.	Liver of ox or sheep, glycerin, alcohol, water.	95	1 oz. equal to 8 oz. fresh liver	1 oz. 30 ml.
Hyoscyami Liq.	Hyoscyamus powder 1000 grm., alcohol q.s.	70	0.05 p.c. of alkaloids	3 to 6 ms. 0.2 to 0.4 ml.
Ipecacuanhae Liq.	Ipecac. powder 1000 grm. alcohol q.s.	80	2 p.c. emetine	1/2 to 2 ms. or 10 to 30 ms.
Nucis Vomicae Liq.	Nux vomica 1000 grm., alcohol q.s.	45 and 70	1.5 p.c. strychnine	1 to 3 ms. 0.06 to 0.2 ml.
Quillaia Liq.	Quillaia, 1000 grm.; alcohol, q.s. 1000 ml.	45	..	..
Senegae Liq.	Senega 1000 grm., dilute solution of ammonia q.s. alcohol q.s. to 1000 ml.	60	50 p.c.	5 to 15 ms. 0.3 to 1 ml.
Sennae Liq.	Senna fruit 1000 grm., alcohol 250 ml., oil of coriander, 6 ml., distilled water and chloroform water each q.s. 1000 ml.	90	50 p.c.	10 to 30 ms. 0.6 to 2 ml.
Stramonii Liq.	Stramonium 1000 grm., alcohol q.s.	45	0.25 p.c. hyoscyamine	1/2 to 3 ms. 0.03 to 0.2 ml.

From the above table it will be gathered that all the liquid extracts, require alcohol of various strengths, either for their preparation or for their preservation. Extract of Male Fern being prepared with ether is given in the table of **Ethereal Extract.**

In the preparation of liquid extract of colchicum, the seeds are first treated with light petroleum to remove fat before adding alcohol; while ergot is treated with light petroleum to remove fat and then the liquid extract is prepared with alcohol acidified with tartaric acid.

The *strength* of liquid extracts not containing any potent principle is so adjusted that one part by weight of the drug produces one part by volume of the finished product, *i. e.*, the strength is 1 in 1. In the case of extracts of powerful drugs, the strength is adjusted to a definite percentage of the active principle based on the average percentage of the active principle present in the crude drug. Thus the liquid extract of ipecacuanha is so adjusted that it should contain 2 p.c. *emetine*, *i.e.*, the alkaloid strength contained in ipecacuanha.

N.B.—Extract of male fern, extracts of malt, malt with cod-liver oil are thick viscid liquids, though they are not called liquid extracts in the B.P.

Ethereal Extracts are prepared by percolating dry drugs with ether. There is only one in the B. P.

Extractum	Ingredients	Menstruum	Strength	Dose
Filicis	Male Fern, Olive Oil	Ether	25 p.c. Filicin.	45 to 90 ms. 8 to 6 mil.

Dry Extracts, sometimes called abstracts, are alcoholic or watery extracts mixed with an inert powdered substance and then dried and powdered. They are nine in number.

Extractum	Ingredients	Strength	Dose
Belladonnae Sicc.	Belladonna herb, alcohol 70 p.c.	1 p.c. Alkaloids	1/4 to 1 gr. 15 to 60 mg.
Cascarae Sagradae Sicc.	Powdered cascara sagrada and water.	..	2 to 8 gr. 0.12 to 0.5 G.
Colchici Sicc.	Colchicum corm 1000 G., alcohol (60 p.c.) and lactose each q.s.	1 p.c. colchicine	1/6 to 1/2 gr. 10 to 30 mg.
Colocynth. Co.	Colocynth 27 G., aloes 56 G., ipomoea resin 18½ G., curd soap powder 14 G., cardamom 4½ G., alcohol (60 p.c.) 700 ml.	27 p.c.	2 to 8 gr. 0.12 to 0.5 G.
Hamamelidis Sicc.	Hamamelis, alcohol (45 p.c.)	..	..
Hyoscyami Sicc.	Hyoscyamus 1000 G., alcohol (70 p.c.) q.s.	0.3 p.c. alkaloid	1/4 to 1 gr. 16 to 60 mg.
Krameriae Sicc.	Krameria, water.	..	5 to 15 gr. 0.3 to 1 G.
Nucis Vomicae Sicc.	Nux vomica 1000 G., alcohol (70 p.c.) calc. phosphate each q. s.	5 p.c. strychnine	1/4 to 1 gr. 15 to 60 mg.
Stramonii Sicc.	Stramonium 1000 G., alcohol (95 p.c.), starch, each q.s.	8/100 gr. hyoscyamine in 8 gr.	1/4 to 1 gr. or 1 to 8 gr.

The following extracts are standardized :—

Ext. Belladonnae Liq.	Ext. Hyoscy. Sicc.
” ” Sicc.	” Ipecac. Liq.
” Colchici Liq.	” Nucis Vom. Liq.
” ” Sicc.	” ” ” Sicc.
” Ergot. Liq.	” Stramonii Liq.
” Hyoscy. Liq.	” ” Sicc.

Gelatinum.—Gelatin pastes are mixtures of gelatin, glycerin and water in varying proportions, and are non-irritating protectives to the skin. They should be melted before use and applied with a brush. There is only one preparation.

Gelatinum Zinci. *Syn.—Unna's Paste.*—Zinc oxide, gelatin cut small, each 150 grm., glycerin 350 grm., distilled water 350 mils or q. s.

Glycerina.—Glycerins are solutions of drugs in plain glycerin or glycerin and water. Because of the high viscosity of glycerin these preparations adhere to the mucous surface over which they are applied, therefore they are very popular as throat application where the demulcent action of glycerin also comes into play. Phenol having greater affinity for glycerin than water, Glycerinum Phenolis does not act as a caustic. They are five in number.

Glycerinum	Ingredients	Action
Acidi Borici	Boric acid 31 G., glycerin q.s. to 100 G.	Antiseptic
Acidi Tannici	Tannic acid 15 G., glycerin 85 G.	Astringent
Amyli	Starch 85 G., water 170 mils, glycerin 745 G.	Emollient
Boracis	Borax 12 G., Glycerin 88 G.	Antiseptic emollient
Phenolis	Phenol 16 G., glycerin 84 G.	Antiseptic

Infusa.—Infusions are of three varieties, (a) *Plain Infusions*, prepared by diluting concentrated infusions, (b) *Concentrated Infusions*, and (c) *Fresh Infusions* (Recens).

Infusum	Preparation	Dose
Aurantii	Concentrated infusion of orange peel, 125 ml. ; water, q. s. 1000 ml.	1/2 to 1 oz. or 15 to 30 mil.
Calumbae	Concentrated infusion of calumba 125 ml. ; water q. s. 1000 mil.	1/2 to 1 oz. or 15 to 30 mil.
Caryophylli	Concentrated infusion of clove 125 mil. ; water, q. s. 1000 mil.	1/2 to 1 oz. or 15 to 30 mil.
Gentianae Co.	Concentrated compound infusion of gentian 125 mil. ; water, q. s. 1000 mil.	1/2 to 1 oz. or 15 to 30 mil.
Quassiae	Concentrated infusion of quassia, 125 mil. ; water, q. s. 1000 mil.	1/2 to 1 oz. or 15 to 30 mil.
Senegae	Concentrated infusion of senega 125 mil. ; water, q. s. 1000 mil.	1/2 to 1 oz. or 15 to 30 mil.
Sennae	Concentrated infusion of senna, 125 mil. ; water, q. s. 1000 mil.	1/2 to 2 oz. or 15 to 60 mil.

Infusa Concentrata. Concentrated infusions are solutions of drugs in alcohol prepared either by percolation or maceration, to be diluted with seven times their volume of distilled water, when they become approximately equivalent in strength, but not in flavour, to fresh infusions, but containing only a small proportion of alcohol. They are seven in number.

Infusum	Ingredients	Dose
Aurantii Conc.	Dried bitter orange peel 400 grm., alcohol (25 p.c.) 1050 mils.	2 to 4 mils. 30 to 60 ms.
Calumbae Conc.	Calumba cut small 400 grm., alcohol (90 p.c.) 250 mils, distilled water q.s. to 1000 mils.	2 to 4 mils. 30 to 60 ms.
Caryophylli Conc.	Clove bruised 200 grm., alcohol (25 p.c.) 1100 mils.	2 to 4 mils. 30 to 60 ms.
Gentianae Compositum Conc.	Gentian sliced 100 grm., dried bitter-orange peel 100 grm., lemon peel 100 grm., alcohol (25 p.c.) 1200 mils.	2 to 4 mils. 30 to 60 ms.
Quassiae Conc.	Quassia rasped 80 grm., alcohol (90 p.c.) 250 mils., distilled water q.s. to 1000 mils.	2 to 4 mils. 30 to 60 ms.
Senegae Conc.	Senega 400 grm., dilute solution of ammonia and alcohol (25 p.c.) each q.s. to 1000 mils.	2 to 4 mils. 30 to 60 ms.
Sennae Conc.	Senna fruit 800 grm., strong tr. of ginger 80 mils., alcohol (20 p.c.) q.s. to 1000 mils.	2 to 8 mils. 30 to 120 ms.

Infusum Recens, Fresh infusion.—There are two in the B. P.

Infusum Calumbae Recens.—Calumba, cut small, 5 G. ; *cold water*, 100 mil. *Infused for half an hour.* **Dose.**—1/2 to 1 oz. or 15 to 30 ml.

Infusum Quassiae Recens.—Quassia, rasped, 10 G. ; *cold water* 1000 mil. Infused *for fifteen minutes.* **Dose.**—1/2 to 1 oz. or 15 to 30 ml.

All infusions, except concentrated infusions should be used within twelve hours of their preparation.

Injectio.—Injections are solutions or suspensions of drugs for

injection either subcutaneously, intramuscularly or intravenously. They are seventy-five in number.

Injectio	Ingredients	Dose
Adrenalinae	Adrenaline 0.1 G., tartaric acid 0.08 G., sodium metabisulphite 0.1 G., sodium chloride 0.8 G., water for injection, q.s. 100 mil.	2 to 8 ms. or 0.12 to 0.5 ml.
Aethanolaminae Oleatis	Ethanolamine 0.91 G., oleic acid 4.23 G., benzyl alcohol 2.0 mil. water for injection q.s. 100 mil.	*Intravenously* as a sclerosing agent : 30 to 75 ms.
Amethocainae Hydrochlor.	Amethocaine hydrochlor., and injection of sodium chloride.	....
Aneurinae Hydrochlor.	Sterile solution of aneurine hydrochlor., water for injection.	1/6 to 1/2 gr. 10 to 30 mg.
Antimonii et Pot. Tart.	Sterile solution of potassium antimonyltartrate and water for injection.	1/2 to 2 gr. 30 to 120 mg.
Antimonii et Sod. Tart.	Sterile solution of sodium antimonyltartrate and water for injection.	1/2 to 2 gr. 30 to 120 mg.
Apomorphinae Hydrochlor.	Sterile solution of apomorphine hydrochlor, and water for injection.	1/32 to 1/8 gr. 2 to 8 mg.
Atropinae Sulph.	Sterile solution of atropine sulphate in water for injection.	1/240 to 1/60 gr. 0.25 to 1 mg.
Bismuthi	Precipitated bismuth 5 G., dextrose 1.25 G., chlorocresol 0.025 G., water for injection 23.5 mil. 3 gr. in 15 ms.	8 to 15 ms. 0.5 to 1 ml.
Bismuthi et Sodii Tart.	Sterile solution of sodium bismuthyltartrate in water for injection.	1 to 3 gr. 60 to 200 mg.
Bismuthi Oxychloridi	Bismuth oxychloride 10 grm., dextrose 5 grm., chlorocresol, 0.2 grm., water for injection q.s. to 100 mils.	15 to 30 ms. 1 to 2 mils.
Bismuthi Salicylatis	Bismuth salicylate 10 grm. ; camphor and phenol, each 1 grm. arachis oil q.s. to 100 mils.	10 to 20 ms. 0.6 to 1.2 mils.
Caffeinae et Sod. Benz.	Sterile solution of caffeine and sodium benzoate in water for injection.	2 to 5 gr. 0.12 to 0.3 G.
Calcii Gluconatis	Calc. glucon. 10 grm., water for injection 95 mil.	150 to 300 ms. 10 to 20 mil.
Carbacholi	Sterile solution of carbachol in water for injection.	1/240 to 1/120 gr. 0.25 to 0.5 mg.
Deoxycortoni Acetatis	Sterile solution of deoxycortone acetate in ethyl oleate or a suitable oil.	1/30 to 1/6 gr. 2 to 10 mg. *intramuscularly*
Dextrosi	Sterile solution of dextrose in water for injection (5.0 p. c.).	..
Digoxini	Alcoholic solution of digoxin (digoxin 50 mg., alcohol (70 p.c.) 100 mil.) Add 1 mil of this solution to 9 mil of injection of sodium chloride.	150 to 300 ms. 10 to 20 mil. *Intravenously.*
Diodoni	Sterile aqueous solution of diethanolamine salt of 3 : 5-diiodo-4-pyridone-*N*-acetic acid.	*Adult* : 300 ms. or 20 mil. *Child* : 120 to 150 ms. 8 to 10 mil. *Infant* : 30 to 45 ms. 2 to 3 mil.
Emetinae Hydrochlor.	Sterile solution of emetine hydrochloride in water for injection.	1/2 to 1 gr. or 30 to 60 mg. daily.
Ergometrinae Maleatis	Sterile solution of ergometrine maleate in water for injection.	*Intramuscular* :— 1/240 to 1/120 gr. 0.25 to 0.5 mg. *Intravenous* :—1/480 to 1/240 gr. 0.125 to 0.25 mg.
Gonadotrophini Chorionici	Sterile solution chorionic gonadotrophin in water for injection with 0.5 p.c. w/v phenol.	100 to 500 Units *Intramuscular.*
Gonadotrophini Serici	Sterile solution of serum gonadotrophin in water for injection with 0.5 p.c. phenol.	200 to 1000 Units. *Intramuscular.*
Heparini	Sterile solution of heparin in injection of sodium chloride.	6000 to 12000 Units *intravenously.*
Hexobarbitoni Sodii	Sterile solution of hexobarbitone sodium in water for injection which is free from CO_2.	3 to 15 gr. 0.2 to 1 G. intravenous or intramuscular injection.

Injectio	Ingredients	Dose
Histaminae Phosph. Acidi	Sterile solution of histamine acid phosphate in water for injection.	1/120 to 1/60 gr. 0.5 to 1 mg. *Subcutaneously.*
Hyoscinae Hydrobromidi	Sterile solution of hyoscine hydrobromide in water for injection.	1/200 to 1/100 gr. 0.3 to 0.6 mg. Subcutaneously.
Insulini	Sterile solution of the specific antidiabetic principle of the mammalian pancreas, containing 20, 40, or 80 Units per mil.	Determined by the physician.
Insulini Protaminat. cum Zinco	Sterile suspension of the specific antidiabetic principle of the mammalian pancreas with a suitable protamine and zinc chloride, containing 40 or 80 Units per mil.	Determined by the physician.
Iodoxyli	Sterile solution of iodoxyl in water for injection.	150 to 225 gr. 10 to 15 G. *Intravenously.*
Leptazoli	Leptazol, 10 G.; sodium phosphate, 0.25 G.; water for injection, q.s. 100 mil.	8 to 15 ms. or 0.5 to 1 mil. *Subcutaneously.*
Menaphthoni	Sterile solution of menaphthone in ethyl oleate or a suitable oil.	1/60 to 1/12 gr. 1 to 5 mg. daily.
Mepacrinae Methanosulphonatis	Sterile solution of mepacrine methanesulphonate in water for injection.	1½ to 5 gr. 0.1 to 0.3 G. *Intramuscularly.*
Mersalyli	Mersalyl, 10 G.; theophylline, 5 G.; solution of potassium hydroxide, q.s.; water for injection, q.s. 100 mil. 8 gr. mersalyl and 1½ gr. theophylline in 30 ms.	8 to 30 ms. 0.5 to 2 mil. *Intravenous or intramuscular injection.*
Morphinae et Atropinae	Atropine sulphate, 0.06 G.; morphine sulphate, 1 G.; water for injection q.s. 100 mil. 1/100 gr. atropine sulphate and 1/6 gr. morphine sulphate in 15 ms.	8 to 15 ms. 0.5 to 1 mil. *Subcutaneously.*
Morphinae Sulph.	Sterile solution of morphine sulphate in water for injection.	1/8 to 1/3 gr. 8 to 20 mg. *Subcutaneously.*
Neoarsphenaminae	Solution of neoarsphenamine in water for injection.	2½ to 10 gr. 0.15 to 0.6 G. *Intravenously.*
Neostigminae Methylsulph.	Sterile solution of neostigmine methylsulphate in water for injection.	1/120 to 1/30 gr. 0.5 to 2 mg. *Subcutaneously or intramuscularly.*
Nikethamidi	Nikethamide, 25 G.; water for injection, q.s. 100 mil. Contains 15 gr. in 60 ms.	15 to 60 ms. 1 to 4 mil. *Subcutaneous, intramuscular or intravenous.*
Oestradiolis Diprop.	Sterile solution of oestradiol dipropionate in ethyl oleate or a suitable oil.	1/60 to 1/12 gr. 1 to 5 mg. daily.
Oestradiolis Monobenzoatis	Sterile solution of oestradiol monobenzoate in ethyl oleate or a suitable oil.	1/60 to 1/12 gr. 1 to 5 mg. daily
Olei Hydnocarpi	Hydnocarpus oil sterilised by heating	30 ms. (2 ml.) increased to 75 ms. (5 ml.).
Olei Hydnocarpi Aeth.	Ethyl esters of hydnocarpus oil sterilised by heating at 150°.	30 ms. (2 ml.) increased to 75 ms. (5 ml.).
Ouabaini	Sterile solution of ouabain in water for injection.	1/500 to 1/240 gr. 0.12 to 0.25 mg. *intravenously.*
Oxytocini	Sterile aqueous solution of the oxytocic principle from the posterior lobe of the pituitary bodies of oxen or other mammals. Contains 10 Units per mil.	8 to 15 ms. (5 to 10 Units) *by subcutaneous or intramuscular injection.*
Penicillini	Sterile solution of penicillin (sodium or calcium salt) in water for injection. 50,000 Units per mil.	To be determined by the physician.
Penicillini Cerosa	Penicillin (calcium salt), q.s.; white bees wax, 4.5 G.; arachis oil or ethyl oleate, q.s. 100 mil. 125,000 Units per mil.	To be determined by the physician.
Pethidinae Hydrochlor.	Sterile solution of pethidine hydrochloride in water for injection.	2/5 to 1½ gr. 25 to 100 mg. *Subcutaneously.*

Injectio	Ingredients	Dose
Phenobarbitoni Sodii	Sterile solution of phenobarbitone sodium in water for injection.	1 to 3 gr. (60 to 200 mg.). *Single dose. Intramuscular or intravenous*
Physostigminae Salicylatis	Sterile solution of physostigmine salicylate in water for injection. Contains 0.05 p.c. sodium metabisulphite.	1/100 to 1/50 gr. (0.6 to 1.2 mg.). *Subcutaneously.*
Picrotoxini	Sterile solution of picrotoxin in water for injection.	1/100 to 1/20 gr. (0.6 to 3 mg.). *Intravenous or intramuscular.*
Pituitarii Post.	Sterile extract of the posterior lobe of pituitary bodies of oxen or other mammals. Contains 10 Units (oxytocic) per mil.	3 to 8 ms. (2 to 5 Units). *Subcutaneous or intramuscular injection.*
Procainae et Adrenalinae Fortis	Procaine hydrochloride, 2 G.; sodium chloride, 0.5 G.; chlorocresol, 0.1 G.; solution of adrenaline hydrochlor., 2 ml.; sodium metabisulphite, 0.1 G.; water for injection, q.s. 100 ml. Contains 2 p.c. of procaine and adrenaline solution.	..
Procainae et Adrenalinae Mitis	Sterile solution of procaine hydrochlor. (2 p.c. w/v), 250 ml.; injection of sodium chloride, 750 ml.; injection of adrenaline, 2 ml.	..
Progesteroni	Sterile solution of progesterone in ethyl oleate or a suitable oil.	1/60 to 1/3 gr. (1 to 20 mg.) daily
Quininae Dihydrochlor.	Sterile solution of quinine dihydrochlor. in water for injection.	5 to 10 gr. (0.3 to 0.6 G.). *Intravenously*
Quininae et Urethani	Quinine hydrochloride, 13.3 G.; urethane, 6.25 G.; water for injection, q.s. 100 ml.	8 to 75 ms. (0.5 to 5 ml.) as a sclerosing agent, intravenously.
Sodii Aurothiomalatis	Sterile solution of sodium aurothiomalate in water for injection.	1/6 gr. (10 mg.) gradually increased to 1½ gr. (100 mg.)
Sodii Bicarbonatis	Sterile solution of sodium bicarbonate in water for injection.	..
Sodii Chloridi	Sodium chloride, 9 G.; water for injection, q.s. 1000 ml.	..
Sodii Chloridi Co.	Sodium chloride, 8.6 G.; potassium chloride, 0.3 G.; hydrated calcium chloride, 0.48 G.; water for injection, q.s. 1000 ml.	..
Sodii Citratis Anticoag.	Sodium citrate, 25 G.; sodium chloride, 9 G.; water for injection, q.s. 1000 ml.	..
Sodii Citratis cum Dextroso	Sodium citrate and dextrose, each 30 G.; water for injection, q.s. 1000 ml.	..
Sodii Lactatis Co.	Sodium hydroxide, q.s.; acid lactic, 2.4 ml.; sodium chloride, 6 G.; potassium chloride, hydrated calcium chloride, each 0.4 G.; water for injection, q.s. 1000 ml.	
Stibopheni	Stibophen, 6.4 G.; sodium metabisulphite, 0.1 G.; water for injection, q.s. 100 ml.	25 to 75 ms. (1.5 to 5 ml.) intramuscularly.
Strychninae Hydrochlor.	Sterile solution of strychnine hydrochloride in water for injection.	1/30 gr. (2 mg.) to 1/16 (4 mg.). *Subcutaneously.*
Sulphadiazinae Sodii	Sterile solution of sulphadiazine sodium in water for injection.	5 to 30 gr. (0.3 to 2 G.) intravenously.
Sulpharsphenaminae	Solution of sulpharsphenamine in water for injection.	1½ to 10 gr. (0.1 to 0.6 G.) *Subcutaneous or intramuscular injection.*
Sulphathiazoli Sodii	Sterile solution of sulphathiazole sodium in water for injection.	5 to 30 gr. (0.3 to 2 G.). *Intravenously.*
Suramini	Sterile solution of suramin in water for injection.	15 to 30 gr. (1 to 2 G.). *Intravenous.*
Testosteroni Propionatis	Sterile solution of testosterone propionate in ethyl oleate or a suitable oil.	1/12 to 1/3 gr. (5 to 20 mg.) daily.

Injectio	Ingredients	Dose
Theophyllinae c. Aethylene-diamina	Sterile solution of theophylline with ethylenediamine in water for injection.	1½ to 8 gr. (0.1 to 0.5 G.). *Intravenous* or *intramuscular.*
Thiopentoni Sodii	Sterile solution of thiopentone sodium in water for injection.	1½ to 8 gr. (0.1 to 0.5 G.). *Intravenously.*
Tryparsamidi	Sterile solution of tryparsamide in water for injection.	15 to 30 gr. (1 to 2 G.). *Subcutaneous, intramuscluar or intravenous.*
Vasopressini	Sterile aqueous solution containing the pressor and antidiuretic principles from the posterior lobe of the pituitary bodies of oxen or other mammals.	8 to 25 ms. or (5 to 15 Units). *Subcutaneous or intramuscular.*

Lamellae.—Eye-discs are thin plates or discs of medicated gelatin with glycerin, used in ophthalmic practice. These are prepared by dissolving gelatin 18 gms., in glycerin 2 gms., and water 88 gms. or *q.s.* They are four in number.

Lamellae	Composition	Strength in each	Action
Atropinae	Discs of gelatin with glycerin weighing about 1/50 gr. each.	1/5000 gr.	Mydriatic
Cocainae	Discs of gelatin with glycerin weighing about 1/20 gr. each.	1/50 gr.	A local anaesthetic
Homatropinae	Discs of gelatin with glycerin weighing about 1/32 gr. each.	1/100 gr.	Mydriatic
Physostigminae	Discs of gelatin with glycerin weighing about 1/50 gr. each.	1/1000 gr.	Myotic

Linimenta.—Liniments or **Embrocations** are preparations used for rubbing or painting over the skin. The majority of them are limpid liquids. Camphor enters into their composition for its local stimulant action, and also to lessen the risk of these being taken internally as it has a characteristic strong smell. They are six in number.

Linimentum	Composition	Strength	Action and uses
Aconiti	Aconite 50 grm., camphor 3 grm., alcohol (90 p.c.), q.s. 100 mils.	50 p.c.	A powerful local sedative and anodyne
Belladonnae	Belladonna root 1000 grm., camphor, alcohol (80 p.c.), each q.s. to produce the required strength.	0.375 p.c. alkaloids	A powerful local anodyne. In neuralgia, etc.
Camphorae	Camphor 2 grm., and arachis oil 8 grm.	20 p.c.	A local stimulant
Camphorae Ammoniatum	Camphor 125 grms., oil of lavender 5 mils., strong solution of ammonia 250 mils., and alcohol (90 p.c.) to 1000 mils.	12.5 p.c.	Rubefacient and counter-irritant
Saponis	Soft soap 80 grms., camphor 40 grms., oil of rosemary 15 mils, alcohol (90 p.c.) q.s. to 1000 mils, and water 170 mils.	8 p.c.	A stimulant application to sprains and bruises
Terebinthinae	Soft soap 75 grms., camphor 50 grms., oil of turpentine 650 mils, water q.s. to 1000 mils.	65 p.c.	Irritant and rubefacient

Liquores.—Solutions are solutions of vegetable, animal or inorganic substances in a suitable vehicle, such as distilled water,

alcohol, oil, or with other solvents. Liq. Adrenalinae Hydrochlor. is obtained from the animal kingdom. They are twenty-eight in number. Of these four are Vitamin preparations, the solvent being an oil. These will be considered separately.

Liquor	Composition	Strength	Dose
Adrenalinae Hydrochlor.	Adrenaline 1 G., chlorbutol 5 G., sodium chloride 9 G., sod. metabisulphite 0.5 G.; acid. hydrochloric dil. 2 ml., water q.s. to 1000 ml.	1 in 1000 or 0.1 p.c.	...
Ammoniae Dil.	Strong solution of ammonia 300 mls., water q.s. 1000 ml.	10 p.c. w/w	...
Ammoniae Fortis	———	32.5 p.c. by weight	Used externally
Ammonii Acetatis Dil.	Strong solution of ammon. acet. 125 ml., water q.s. to 1000 ml.	7.2 p.c.	1/4 to 1 oz. 8 to 30 ml.
Ammonii Acetatis Fortis	Acid acetic glacial 450 G., ammon. bicarb. 470 G., liq. ammon. fort. 100 ml. or q.s. water q.s. 1000 ml.	57.5 p.c.	15 to 60 ms. 1 to 4 ml.
Arsenicalis	Arsenic trioxide 10 G., liq. pot. hydrox. 100 ml., acid hydrochloric dil. 25 ml. or q.s. water 1000 mls.	1 p.c.	2 to 8 ms. 0.12 to 0.5 ml.
Calcii Hydroxidi	Calcium hydroxide 1 G., water 100 ml.	0.15 p.c.	1 to 4 oz. 30 to 120 ml.
Chloroxylenolis	Chloroxylenol 5 G.; terpineol 10 ml.; alcohol (95 p.c.) 20 ml.; ricinoleic acid, 5 G.; sol. pot. hydrox. q.s. water q.s. 100 ml.	5 p.c.	...
Cresolis Saponatus	Cresol 500 ml., linseed oil 180 G., Pot. hydroxide 42 G., water q.s. to 1000 ml.	50 p.c.	Used externally
Ferri Perchloridi	An aqueous solution of ferric chloride obtained by oxidation of ferrous chloride.	15 p.c. ferric chlor.	5 to 15 ms. 0.3 to 1 ml.
Formaldehydi	An aqueous solution with ethyl or methyl alcohol.	37 to 41 p.c. CH_2O	Used externally
Hydrargyri Perchloridi	Mercuric chloride 1 G., and water q.s. 1000 mls. by solution.	1/16 gr. in 60 ms.	30 to 60 ms. 2 to 4 mls.
Hydrogenii Peroxidi	An aqueous solution of hydrogen peroxide.	5 to 7 p.c. H_2O_2	...
Iodi Aquosus	Iodine 50 G., potassium iodide 100 G., distilled water q.s. 1000 mls.	5 p.c. iodine 10 p.c. pot. iodide	5 to 15 ms. 0.3 to 1 mil.
Iodi Fortis	Iodine 10 G., pot. iodide 6 G., water 10 mls., alcohol (90 p.c.) q.s. to 100 ml.	10 p.c. iodine, 6 p.c. pot. iodide	Used externally
Iodi Mitis	Iodine 2.5 G., pot. iodide 2.5 G., water 2.5 ml., alcohol (90 p.c.) q.s. to 100 ml.	2.5 p.c. iodine, 2.5 p.c. pot. iodide	5 to 30 ms. 0.3 to 2 ml.
Magnesii Bicarbonatis	A solution of mag. bicarbonate in water saturated with CO_2.	10 gr. in 1 oz.	1 to 2 oz. 30 to 60 mls.
Morphinae Hydrochloridi	Morphine hydrochloride 1 G., dilute hydrochloric acid 2 mls., alcohol (90 p.c.) 25 mls. and water q.s. to 100 mls.	1/4 gr. in 30 ms. or 1 p.c.	5 to 30 ms. 0.3 to 2 mls.
Picis Carbonis	Prepared coal tar 2 G., quillaia in powder 1 G., and alcohol (90 p.c.) q.s. to 10 mls.	20 p.c.	Used externally
Plumbi Subacetatis Dil.	Strong lead subacetate solution 12.5 mls., water q.s. to 1000 mls.	1.25 p.c. liquor	Used externally
Plumbi Subacetatis Fortis	Lead acetate 250 G., lead monoxide in powder 175 G., and water q.s. to 1000 mls.	19 to 21.5 p.c. lead	Used externally
Potassii Hydroxidi	An aqueous solution containing 5 p.c. of total alkali, KOH.		Used externally
Sodae Chlorinatae Chirurgicalis	Chlorinated lime, boric acid, sod. carb. each q.s. water 1000 ml.	0.5 to 0.55 p.c. chlorine	Used externally
Strychninae Hydrochloridi	Strychnine hydrochloride 1 G., alcohol (90 p.c.) 25 mls. and water q.s. to 100 mls.	1 p.c. or 1/8 gr. in 12 ms.	2 to 8 ms. 0.12 to 0.5 ml.

The following liquors are all 1 p.c., i.e. contain 1 gr. in 110 ms.:— Liquor arsenicalis, morphinae hydrochlor., strychninae hydrochlor.

The following liquors are meant for external use only:—
Liquor ammoniae fort., Liq. cresolis saponatus, Liq. chloroxylenolis, Liq. formaldehydi, Liq. iodi fort., Liq. picis carbonis, Liq. plumbi subacetatis fort., and dilutus, Liq. potassii hydroxidi, and Liq. sodae chlorinatae chirurgicalis.

Liquors Containing Vitamin A and D

Liquor Calciferolis is a [illegible] p.c. [illegible] of calciferol in [illegible] vegetable oil, such as arachis oil. Contains [illegible] Units vitamin D in 1 G. Dose—Prophylactic [illegible] Units daily. Therapeutic [illegible] Units daily.

Liquor Vitamini A Concentratus is a solution of vitamin A containing in 1 gm. [illegible] units. May consist of a suitable fish-liver oil or blend of fish-liver oils, or prepared from a source of vitamin A dissolved in some vegetable oil, such as arachis oil. Dose—[illegible] Units daily.

Liquor Vitamini D Concentratus is a solution of vitamin D containing in 1 gm. [illegible] units of antirachitic activity. Prepared in the same way as concentrated solution of vitamin A. Dose—Prophylactic [illegible] Units daily. Therapeutic [illegible] Units daily.

Liquor Vitaminorum A et D Concentratus is a solution containing in 1 gm. [illegible] units of vitamin A activity and [illegible] units of antirachitic activity (vitamin D). May consist of a suitable fish-liver oil or blend of fish-liver oils, or prepared by dissolving a source of vitamin A and vitamin D, in a suitable vegetable oil, such as arachis oil. Dose—[illegible] of vitamin A ([illegible] Units) + vitamin D ([illegible] Units).

Lotiones.—Lotions are solutions or mixtures of active ingredients for external application only. There is only one.

Lotio Calaminae.—*Calamine Lotion.*—Calamine [illegible] G.; zinc oxide, [illegible] G.; glycerin, [illegible] ml.; water, q.s. 1000 ml.

Mella.—Mellita. Honeys are liquid preparations containing honey as a vehicle. They are three in number.

Mel Depuratum is honey melted and strained through flannel after allowing scum to rise to the surface.

Mel	Preparation	Strength	Dose	Action
Oxymel	Acetic Acid 15, water 15, honey q.s. to 100 ml.	—	[illegible] ms. ([illegible] 8 mils.)	Expectorant. Used as a vehicle
Oxymel Scillae	Squill 5 gm., acetic acid 9 ml., water 25 ml., honey q.s.	5 p.c. squill	[illegible] ms. (2 to 4 mils.)	Expectorant.

Misturae.—Mixtures are preparations in which drugs are simply dissolved in water or suspended in it. The official mixtures are only two in number.

Mistura	Preparation	Strength	Dose
Magnesii Hydroxidi (Cream of Magnesia)	Mag. Sulph. [illegible] G., sodium hydroxide 15 G., light mag. oxide 52.5 G., water q.s. 1000 ml.	[illegible] gr. MgO in 240 ms.	[illegible] ms. 4 to 16 mils.
Sennae Composita	Magnesium sulphate 25 G., liquid extract of liquorice 5 mils, tinct. cardam. co. 10 mils., sp. ammon. aromat. 5 mils., and fresh infusion of senna q.s. to 100 mils.	[illegible] grs. in 1 oz. or 25 p.c. mag. sulph.	1 to 2 ozs. 30 to 60 mils.

Mucilagines.—Mucilages are solutions of gummy substances in water. They are two in number.

Mucilago	Ingredients
Acaciae	Acacia 40 G., chloroform water 60 ml.
Tragacanthae	Tragacanth [illegible] G., alcohol ([illegible] p.c.) [illegible] mls., chloroform water q.s. to 1000 ml.

Oculenta.—**Eye Ointments** are preparations meant for application to the eye. They are prepared as follows :—

Melt together 90 parts by weight of yellow soft paraffin and 10 parts by weight of wool fat, filter while hot and sterilise by heat at 150°C. for one hour. The drug required for 100 grms. is mixed in a sterile mortar and the melted basis added to weigh 100 grms.

Oculentum	Ingredients	Strength
Atropinae	Atropine sulphate.	0.25 p.c.
Atropinae c. Hydrargyri Oxido	Atropine sulphate, yellow mercuric oxide.	0.125 p.c. 1 p.c.
Cocainae	Cocaine hydrochloride	0.25 p.c.
Hydrargyri Oxidi	Yellow mercuric oxide	1 p.c.
Hyoscinae	Hyoscine hydrobromide	0.125 p.c.
Penicillini	Penicillin (calcium salt)	1000 Units in 1 grm.
Physostigminae	Physostigmine salicylate	0.125 p.c.

Oleata.—**Oleates** are preparations of bases with oleic acid, having a solid or semi-solid consistence. Only one preparation, viz. :—

Hydrargyrum Oleatum.—Yellow mercuric oxide 20 gms., liquid paraffin 5 gms., oleic acid 75 gms.

Olea. Oils.—There are thirty oils in the B. P. They can be grouped under two classes—fixed and volatile, except **Oleum Iodisatum** which is an iodine addition product of poppy-seed oil ; the former being obtained by expression ; and the volatile by distillation, except lemon oil which is a volatile oil though obtained by expression. Oil of cade is obtained by dry or destructive distillation.

Of the eleven fixed oils, cod-liver oil and halibut-liver oil are animal products and the rest are expressed at ordinary temperatures. Oil of theobroma is solid in cold weather and semi-solid or fluid in hot weather. The colour of cajuput is deep-green and that of cade is almost black. Oil of turpentine is almost colourless. The rest display various shades of straw, yellow and pale-brown.

Fixed or Expressed Oils

Oleum	Source	Dose	Uses
Amygdalae	Bitter or sweet almonds	1/2 to 1 oz.	Demulcent
Arachis	Seeds	..	Emollient
Gossypii Seminis	Seeds	..	Emollient and demulcent
Hippoglossi	Extracted from fresh liver of the Halibut	1 to 8 ms. 1500 to 12,000 units vitamin A.	Nutritive
Hydnocarpi	Seeds. By cold expression	5 to 15 ms up to 60 ms.	In leprosy
Lini	Linseed	..	Demulcent and emollient
Morrhuae	Fresh liver of Cod	60 to 180 ms. daily.	Nutritive, tonic and alterative
Olivae	Ripe fruit	1/2 to 1 oz.	Emollient
Ricini	Fresh seeds	60 to 240 ms.	Cathartic
Sesami	Seeds	..	Emollient
Theobromatis	Roasted seeds	..	For making suppositories

VOLATILE, ESSENTIAL, OR DISTILLED OILS

Oleum	Source	Dose	Uses
Amygdalae Volatile Purificatum	Bitter almond, peach kernel or apricot kernel	..	Flavouring agent
Anethi	Dill fruit	1 to 3 ms.	Carminative
Anisi	Anise or star anise	1 to 3 ms.	Do
Cadinum	Woody portions ; by destructive distillation	Used externally	A stimulating application
Cajuputi	Fresh Leaves	1 to 3 ms.	Antispasmodic Carminative
Cari	Caraway fruit	1 to 3 ms.	Antispasmodic
Caryophylli	Cloves	1 to 3 ms.	Do
Chenopodii	Fresh plants	3 to 15 ms.	Anthelmintic
Cinnamomi	Cinnamon	1 to 3 ms.	Antispasmodic
Coriandri	Coriander fruit	1 to 3 ms.	Do
Eucalypti	Fresh leaves	1 to 3 ms.	Antiseptic
Hydnocarpi Aethylicum	Esterifying fatty acids of hydnocarpus oil with ethyl alcohol and subsequent distillation	5 to 15 ms. increasing to 60 ms.	In leprosy
Lavandulae	Fresh flowering tops	..	Flavouring agent
Limonis	Fresh lemon peel by expression	..	Aromatic
Menthae Piperitae	Fresh flowering tops	1 to 3 ms.	Antispasmodic and carminative
Myristicae	Nutmeg	1 to 3 ms.	Carminative
Rosmarini	Flowering plant	..	Rubefacient
Terebinthinae	From oleo-resin, turpentine	3 to 10 ms.	Rubefacient

The dose of most of the volatile oils is from **1 to 3 ms.** or **0.06 to 0.2 mil** with the exception of oil of chenopodium, **3 to 15 ms.**; oil of turpentine, **3 to 10 ms.**

Volatile oils are combined with many B.P. pills, either for their carminative effect or because of their smell to serve as a means of distinction between various pill masses of similar appearance.

Pasta. **Pastes** are prepared like ointments and intended for external application. They are usually spread on lint and covered with a layer of cotton wool and kept in position by bandage or adhesive plaster. There is one in the B.P.

Pasta Zinci Oxidi Co.—Zinc oxide and starch, each 250 grms., white soft paraffin 500 grms.

Pilulae.—Pills are solid or semi-solid globular masses containing medicinal agents intended to be swallowed whole without chewing. Pills are always popular for easy administration, being portable, easily swallowed and containing a definite and correct dose. They should not be too hard unless intended to dissolve slowly, or so soft as to lose shape and stick together. To prevent this and to cover the nauseous taste they are coated or gilded. In India and tropical countries, pills get too hard or too soft according to the variations of the weather ; being liable to become soft and to run together during the rains. To avoid this, they should be kept in well-stoppered bottles. Pills, as a rule, should not weigh more than 5 grains each. A mass of the consistence of firm clay is first made by pounding and kneading the drugs together in a mortar ; and subsequently this mass is either rolled and divided by a pill-making machine, or when the quantity is small, the same process is done over a pill-tile by the spatula. The pills should be perfectly round and firm. The B.P. pills are five in number.

Pilula	Composition	Strength
Aloes	Aloes 58 G., hard soap 29 G., oil of caraway 3 mils., syr. of glucose 10 G. or q.s.	58 p.c.
Colocynthidis et Hyoscyami	Colocynth 12.5 G., aloes 25 G., ipomoea resin 25 G., oil of clove 4 ml., curd soap 7 G., ext. hyoscy. sicc. 12.5 G., syrup of glucose 14 G. or q.s.	12.5 p.c.
Ferri Carbonatis	Exsiccated ferrous sulphate 34 G., exsiccated sodium carbonate 21.6 G., acacia 8.4 G., tragacanth 2 G., liquid glucose 32 G., and water 2 mils.	20 p.c. (Ferrous Carb.)
Hydrargyri	Mercury 33 G., syrup 14 G., liquid glucose 15 G., glycerin 5 G., liquorice 33 G.,	33 p.c.
Rhei Co.	Rhubarb 25, powder aloes 20, myrrh 14, hard soap 14, oil of peppermint 2, syrup of glucose 25, or q.s.	25 p.c.

All the cathartic pills in the above table contain aloes except the mercurial pill. All pills are given in 4 to 8 grain doses, except Pil. Ferri Carbonatis, 5 to 30 grs.

Pulverata. Powders of crude drugs intended for internal use. They are single vegetable drugs reduced to a fine powder, assayed and adjusted to contain a definite percentage of active ingredients by addition of lactose the object being to maintain a uniform percentage of active principles. Only one, *viz.*—

Opium Pulveratum, *Dose.*—1/2 to 3 gr. or 30 to 200 mg. 3/10 gr. morphine in 3 gr.

Pulveres.—Powders are mixtures of dry substances reduced to a fine powder and intimately mixed together. Powders should be mixed in a very clean mortar (a glass one being the best). The method of mixing greatly affects the miscibility of powders. The B.P. powders are seven in number.

Pulvis	Composition	Strength	Dose	Action
Cretae Aromaticus	Chalk 25, cinnamon 10, nutmeg 8, clove 4, cardamom 3, sucrose 50	25 p.c.	10 to 60 grs. 0.6 to 4 G.	Aromatic, astringent, and antacid
Cretae Aromat. cum Opio	Aromatic chalk powder 975, opium 25	2.5 p.c. (opium)	10 to 60 grs. 0.6 to 4 G.	Aromatic, astringent
Effervescens Co.	Sodium potassium tartrate 7.5 grm., sodium bicarbonate 2.5 grm., mix, and wrap in blue paper ; tartaric acid in dry powder 2.5 grm., wrap in white paper.	116 38½ & 38½ grs.	193 grs. or 12.5 G.	Hydragogue cathartic
Glycyrrhizae Co.	Senna leaf 16, liquorice 16, fennel 8, sublimed sulphur 8, sucrose 52	16 p.c. Senna	60 to 120 grs. 4 to 8 G.	A mild cathartic
Ipecac. et Opii	Ipecac. powder 1, opium powder 1, lactose 8.	10 p.c. (opium)	5 to 10 grs. 0.3 to 0.6 G.	Diaphoretic anodyne
Rhei Co.	Rhubarb 25, light and heavy magnesium carbonate, each 32.5 and ginger 10.	25 p.c. rhubarb	10 to 60 grs. 0.6 to 4 G.	Antacid, stomachic, cathartic
Tragacanthae Co.	Tragacanth 15, acacia 20, starch 20, and sucrose 45.	15 p.c.	10 to 60 grs. 0.6 to 4 G.	Demulcent

Spiritus. Spirits.—The B.P. spirits, with the exception of Industrial Methylated Spirit, are alcoholic solutions of volatile oils and ethers. They can be divided into two classes—**simple** and **compound.** The simple spirits are solutions of essential oils, ether and chloroform in alcohol (90 p.c.) which often get turbid when diluted with

water. The compound spirits contain more than one ingredient. The B.P. spirits are seven in number, of which five are simple and two compound. The dose of all simple spirits is 5 to 30 ms. or 0.3 to 2 mils, except Spiritus Aetheris, 15 to 60 ms. or 1 to 4 mils.

Simple Spirits

Spiritus	Composition	Strength	Action
Aetheris	Ether and alcohol (90 p.c.)	33 p.c.	A diffusible stimulant, antispasmodic and carminative.
Cajuputi	Oil of cajuput and alcohol (90 p.c.)	10 p.c.	Carminative and antispasmodic
Camphorae	Camphor and alcohol (90 p.c.)	10 p.c.	Stimulant and antispasmodic
Chloroformi	Chloroform and alcohol (90 p.c.)	5 p.c.	A diffusible stimulant and antispasmodic
Menthae Pip.	Oil of peppermint and alcohol (90 p.c.)	10 p.c.	Carminative and antispasmodic

Compound Spirits

Spiritus	Composition	Strength	Dose	Action
Aetheris Nitrosi	Nitric acid, sulphuric acid, copper and alcohol (90 p.c.). By distillation	1.25 to 2.5 p.c. ethyl nitrite	15 to 60 ms. 1 to 4 mils.	Diaphoretic, diuretic, antispasmodic
Ammoniae Aromaticus	Bicarbonate of ammonia 25 gms., strong solution of ammonia 60 mils., oil of nutmeg 3 mils, oil of lemon 5 mils, alcohol (90 p.c.) 750 mils, and distilled water q.s. 1000 mils.		15 to 60 ms. 1 to 4 mils.	Cardiac stimulant, antispasmodic and carminative

Suppositoria.—Suppositories are solid conical-shaped masses containing some active ingredients, for rectal medication. With the exception of the glycerin suppository, all of them are blended with oil of theobroma which melts at 25°C. The melting point may be raised to 37°C. by the addition of white beeswax. They consequently dissolve slowly when introduced into the rectum. They weigh about 15 grains (1 gramme) each. They are ten in number.

Suppositoria	Composition	Strength in each	Action
Acidi Tannici	Tannic acid	3 grs. or 0.2 G.	A local astringent and styptic
Belladonnae	Liquid extract of belladonna 2.5 ms.	1/60 gr. (alkaloids)	A local anodyne
Bismuthi Subgallatis	Bismuth subgallate	5 grs.	Local astringent
Cocainae	Cocaine hydrochlor.	1/4 gr.	Local anaesthetic
Glycerini	Gelatin 14 gms., glycerin 70 gms., and distilled water q.s.	70 p.c. (by weight)	Laxative
Hamamelidis	Dry extract	3 grs.	Haemostatic
Hamamelidis et Zinci Oxidi	Dry extract of hamamelis, zinc oxide	3 grs. and 10 grs.	Astringent and Sedative
Iodoformi	Iodoform	3 grs.	A local antiseptic
Morphinae	Morphine hydrochloride	1/4 gr.	A local anodyne
Phenolis	Phenol	1 gr.	Antiseptic and a local anaesthetic.

Suppositories are used either to produce a local action on the rectum, or on the adjacent pelvic organs such as the uterus and the bladder, or to produce their general effect on the system after absorption.

Syrupi.—Syrups are liquid preparations of drugs containing a sufficient quantity of sucrose, either to preserve them or to make their administration more agreeable. The dose of all syrups is from **30 to 120 ms.** except that of squill which is given in **30 to 60 ms.** No dose is given for syrupus and syrup of glucose. If the concentration of sucrose is less than that in simple syrup, the syrup may undergo fermentation unless some preservative is added. They are ten in number.

Syrupus	Composition	Strength	Action
Syrupus	Sucrose 667 G., water q.s. to 1000 G.	..	A sweetening agent
Aurantii	Tincture of orange 125 mils, syrup q.s. to 1000 mils.	12.5 p.c.	A flavouring agent
Ferri Phosphatis Co.	Iron 4.3 G., phosphoric acid 48 ml., calcium carb. 13.6 G., potassium bicarb. 1 G., sod. phosph. 1 G., cochineal 3.5 G., sucrose 700 G., orange flower water 50 ml., water q.s. to 1000 ml.	1 1/6 gr. ferrous phosph. 1/2 gr. iron & 1¾ gr. tricalcium phosph. in 120 ms.	Haematinic, tonic
Glucosi Liq.	Glucose liquid 333 G., syrup 667 G.	33.3 p.c.	A sweetening agent
Limonis	Lemon peel 60 G., alcohol (60 p.c.), q.s., citric acid 24 G., syrup q.s. to 1000 ml.	6 p.c.	A flavouring agent
Pruni Serotini	Wild cherry bark, 15 G. ; sucrose 80 G. ; glycerin 5 ml. ; water, q.s. 100 ml.	..	Sedative in cough
Scillae	Vinegar of squill 45 mils., sucrose 80 G., water q. s. to 100 mils.	4.5 p.c. squill	Expectorant
Sennae	Liquid extract of senna, 250 ml. ; syrup, q.s. 1000 ml.	25 p.c.	A mild cathartic
Tolutanus	Balsam of tolu 25 G., sucrose 660 G., and water q.s. to 1000 G.	2.5 p.c.	A sweetening agent for cough mixtures
Zingiberis	Strong tincture of ginger 5 ml., syrup q.s. to 100 ml.	5 p.c.	Carminative and antispasmodic

Tabellae. Tablets are solid discs prepared by compressing or moulding a drug, or a mixture of drugs., with or without excipient. They may be prepared either by (a) *Moist Granulation*, (b) *Dry Granulation*, or (c) *Granulation* by preliminary *Compression*. There are forty-nine tablets in the B.P.

Tabellae	Ingredients	Process	Dose	Average Dose
Acetomenaphthoni	Acetomenaphthone	MG & C	1/30 to 1/6 gr.	1/12 gr.
Acidi Acetylsalicylici	Acetylsalicylic acid	DG & C	5 to 15 gr.	5 gr.
Acidi Acetylsalicylici c. Ipecac. et Opio	Acetylsalicylic acid, 162 G. ; ipecacuanha and opium powder, 162 G. for 1000 tablets Contains 2½ gr. each	MG & C	1 to 2 tablets	..
Acidi Acetylsalicylici et Phenacetini	Acetylsalicylic acid, 226.8 G. ; phenacetin, 162.0 G. for 1000 tablets Contains 3½ gr. and 2½ gr.	DG & C	1 to 2 tablets	..
Acidi Ascorbici	Ascorbic acid	MG & C	2/5 to 1¼ gr. or 3 to 8 gr.	3/4 gr.

Tablettae	Ingredients	Process	Dose	Average Dose
Acidi Nicotinici	Nicotinic acid	MG & C	1/4 to 1/2 gr. or 3/4 to 4 gr.	3/4 gr.
Aethisteroni	Ethisterone	MG & C	1/12 to 2/5 gr. daily	1/12 gr.
Aneurinae Hydrochloridi	Aneurine hydrochloride	MG & C	1/60 to 1/20 gr. or 1/6 to 1/2 gr.	1/60 gr.
Atropinae Sulph.	Atropine Sulphate	MG & C	1/240 to 1/60 gr.	1/100 gr
Barbitoni	Barbitone	MG & C	5 to 10 grs.	..
Barbitoni Sodii	Barbitone Sodium	MG & C	5 to 10 grs.	..
Calcii Lactatis	Calcium Lactate	MG & C	15 to 60 grs.	5 grs.
Codeinae Co.	Acetylsalicylic acid, phenacetin, each 259.2 G. ; codeine phosph. 8.1 G. for 1000 tablets Contains 4 gr. each of acid acetylsalicylic and phenacetin, ⅛ gr. codeine phosph.	DG & MG	1 to 2 tablets	..
Codeinae Phosph.	Codeine phosphate	MG & C	1/6 to 1 gr.	1/2 gr.
Dienoestrolis	Dienoestrol	MG & C	1/600 to 1/12 gr.	1/600 gr
Digitalis Praeparatae	Prepared Digitalis	MG & C	1/2 to 1½ gr.	1 gr.
Digoxini	Digoxin	MG & C	1/60 to 1/40 gr. or 1/240 gr.	1/240 gr
Ephedrinae Hydrochlor.	Ephedrine hydrochloride	MG & C	1/4 to 1 gr.	1/2 gr.
Ergotae Praeparatae	Prepared ergot	MG & C	2½ to 8 gr.	2½ gr.
Glycerylis Trinitratis	Glyceryl trinitrate. Chocolate basis	MG & C	1/130 to 1/60 gr.	1/130 gr.
Hexoestrolis	Hexoestrol	MG & C	1/60 to 1/12 gr.	1/60 gr.
Hydrargyri cum Creta	Grey powder	MG & C	1 to 5 grs.	1 gr.
Hydrargyri Subchloridi	Calomel	MG & C	1/2 to 3 grs.	1 gr.
Ipecacuanhae et Opii	Ipecacuanha and opium powder	MG & C	5 to 10 grs.	5 gr.
Mepacrinae Hydrochlor.	Mepacrine hydrochloride	MG & C	*Prophylactic :* 1½ gr. *Therapeutic :* 3 to 8 gr. daily	1½ gr. ..
Methyltestosteroni	Methyltestosterone	MG & C	2/5 to 3/4 gr. daily	1/12 gr.
Methylthiouracili	Methylthiouracil	MG & C	1½ to 3 gr.	1½ gr.
Nicotinamidi	Nicotinamide	MG & C	*Prophylactic :* 1/4 to 1/2 gr. *Therapeutic :* 3/4 to 4 gr.	3/4 gr. ..
Oestroni	Oestrone	MG & C	1/60 to 1/6 gr. daily	1/60 gr.
Phenacetini	Phenacetin	MG & C	5 to 10 gr.	5 gr.
Phenazoni	Phenazone	MG & C	5 to 10 gr.	5 gr.
Phenobarbitoni	Phenobarbitone	MG & C	1/2 to 2 gr.	..
Phenobarbitoni Sodii	Phenobarbitone sodium	MG & C	1/2 to 2 gr.	..
Phenolphthaleini	Phenolphthalein. Chocolate basis	MG & C	1 to 5 gr.	2 gr.
Potassii Bromidi	Potassium bromide	MG & C	5 to 20 gr.	5 gr.
Potassii Chloratis	Potassium chlorate	DG & C	5 to 10 gr.	5 gr.
Quininae Bisulphatis	Quinine bisulphate	MG & C	5 to 10 gr.	5 gr.
Quininae Hydrochloridi	Quinine hydrochloride	MG & C	5 to 10 gr.	5 gr.
Sodii Bicarbonatis Co.	Sodium bicarbonate and oil of peppermint	MG & C	2 to 6 tablets	..
Sodii Citratis	Sodium citrate	M.DG & C	15 to 60 gr.	2 gr.
Sodii Salicylatis	Sodium salicylate	MG & C	10 to 20 gr.	5 gr.
Stilboestrolis	Stilboestrol	MG & C	1/120 to 1/30 gr.	1/120 gr.
Succinylsulphathiazoli	Succinylsulphathiazole	MG & C	45 to 90 gr.	..
Sulphadiazinae	Sulphadiazine	MG & C	30 gr. 1st dose then 15 gr.	

Tabellae	Ingredients	Process	Dose	Average Dose
Sulphaguanidinae	Sulphaguanidine	MG & C	30 to 60 gr.	..
Sulphanilamidi	Sulphanilamide	MG & C	30 gr. followed by 15 gr.	..
Sulphathiazoli	Sulphathiazole	MG & C	30 gr. followed by 15 gr.	..
Thiouracili	Thiouracil	MG & C	1½ to 3 gr.	1½ gr.
Thyroidei	Thyroid	MG & C	1/2 to 2 gr.	1/2 gr.

N. B.—Average dose means the dose that should be dispensed when not mentioned in the prescription.

Tincturae.—Tinctures are alcoholic solutions containing all the active ingredients of the drugs of which they are compounded. In this respect they differ from the official spirits which are merely alcoholic solutions of essential oils. They are prepared either by (*a*) *maceration*, or (*b*) *percolation*. They are twenty-eight in number; of these, only one is from the animal kingdom, viz.:—Tinct. Cocci.

Alcohol of various strengths is used to make tinctures, such as alcohol (90 p.c.), alcohol (70 p.c.), alcohol (60 p.c.), and alcohol (45 p.c.).

The total bulk for all tinctures is 1000 mils with alcohol, or with alcohol and water. The quantities given are for 1000 mils.

Twenty-four tinctures are "Simple" having only one ingredient and one solvent. Four tinctures are called "Compound," having more than one ingredient. Another group of four tinctures are not called compound in the B.P. though they contain more than one ingredient and a solvent. They may be named "Complex."

We shall group tinctures under three heads, viz. :—(1) **Simple, (2) Compound, and (3) Complex.**

SIMPLE TINCTURES

Tinctura	Ingredients	Alcohol p.c. in Menstruum	Process	Strength	Dose
Aurantii	Fresh bitter peel 250 G.	90	M.	25 p.c.	30 to 60 ms.
Belladonnae	Belladonna herb 100 G.	70	P.	0.03 p.c. alkaloids	5 to 15 ms.
Calumbae	Calumba 100 G.	60	M.	10 p.c.	30 to 60 ms.
Capsici	Capsicum 50 G.	60	M.	5 p.c.	5 to 15 ms.
Cocci	Cochineal 100 G.	45	M.	10 p.c.	
Colchici	Liquid extract 100 ml.	60	S.	0.03 p.c. colchicine	5 to 15 ms.
Digitalis	Leaf 100 G. or powdered Leaf 80 G. containing 1000 Units	70	P.	6 Units in 90 ms.	5 to 15 ms.
Hyoscyami	Liquid extract 100 ml.	70	S.	0.005 p.c. alkaloids	30 to 60 ms.
Limonis	Lemon peel 250 G.	60	M.	25 p.c.	30 to 60 ms.
Myrrhae	Myrrh 200 G.	90	M.	20 p.c.	30 to 60 ms.
Nucis Vomicae	Liquid ext. 83.4 ml.	45	S.	0.125 p.c. strychnine	10 to 30 ms.
Opii	Opium 200 G., alcohol q.s., water q.s., to 1000 ml.	90	S.	1 p.c. morphine	5 to 30 ms.
Quassiae	Quassia 100 G.	45	M.	10 p.c.	30 to 60 ms.
Scillae	Squill 100 G.	60	M.	10 p.c.	5 to 30 ms.
Senegae	Liquid extract 200 ml.	60	S.	20 p.c.	30 to 60 ms.

DG=Dry granulation. MG.=Moist granulation. C=Compression.

Tinctura	Ingredients	Alcohol p.c. in Menstruum	Process	Strength	Dose
Stramonii	Liquid extract 100 ml.	45	S.	0.025 p.c. alkaloids	5 to 30 ms.
Strophanthi	Strophanthus 100 G., alcohol 500 ml. or q.s.	70	P.		2 to 5 ms.
Tolutana	Balsam of tolu 100 G.	90	S.	10 p.c.	30 to 60 ms.
Zingiberis Fortis	Ginger 500 G.	90	P.	50 p.c.	5 to 10 ms
Zingiberis Mitis	Strong tincture of ginger 200 ml.	90	S.	..	30 to 60 ms.

Compound Tinctures

Tinctura	Ingredients	Alcohol p.c. in Menstruum	Process	Strength	Dose
Benzoini Co.	Benzoin 100 gms., storax 75 gms., tolu 25 gms., aloes 20 gms.	90	M.	10 p.c.	..
Cardamomi Co.	Cardomom 14 gms., caraway 14 gms., cinnamon 28 gms., cochineal 7 gms., glycerin 50 mils.	60	P.	1.4 p.c.	30 to 60 ms. 2 to 4 mils.
Gentianae Co.	Gentian 100 gms., bitter orange peel 37.5 gms., cardamom seeds 12.5 gms.	45	M.	10 p.c.	30 to 60 ms. 2 to 4 mils.
Rhei Co.	Rhubarb 100 gms., cardamom, coriander, each 12.5 gms., glycerin 100 mils.	60	P.	10 p.c.	30 to 60 ms. 2 to 4 mils

Complex Tinctures

Tinctura	Ingredients	Alcohol p.c. in Menstruum	Process	Strength	Dose
Catechu	Catechu 200 G., cinnamon 50 G., alcohol q.s. to 1000 ml.	45	M.	20 p.c.	30 to 60 ms. 2 to 4 mils.
Ipecacuanhae	Liquid extract 50 ml., alcohol 210 ml., dilute acetic acid 16.5 ml., glycerin 200 ml., water to 1000 ml.	90	S.	0.1 p.c. alkaloids	10 to 30 ms. or 1/2 to 1 oz. emetic.
Opii Camphorata	Tinct. opii 50 ml., benzoic acid 5 G., camphor 3 G., oil of anise 3 ml., alcohol q.s. 1000 ml.	60	S.	0.05 p.c. morphine or 1/30 gr. in 60 ms.	30 to 60 ms. 2 to 4 mils.

Tinctura	Ingredients	Alcohol p.c. in Menstruum	Process	Strength	Dose
Valerianae Ammoniata	Valerian powder 200 G., oil of nutmeg 3 mils., oil of lemon 2 mils., dilute ammonia solution 100 mils., alcohol 900 mils.	60	M.	20 p.c.	30 to 60 ms. 2 to 4 mils.

The following tinctures are standardized :—

Tinct. belladonnae, colchici, hyoscyami, ipecacuanhae, nucis vomicae, opii, opii camphorata and stramonii are standardized by chemical assay.

Tinctures of digitalis and strophanthus are standardized by biological assay.

The dose of most Tinctures is from 30 to 60 ms. except
Ipecacuanha and nux vomica, 10 to 30 ms.
Opium, squill and stramonium, 5 to 30 ms.
Belladonna, capsicum, colchicum and digitalis, 5 to 15 ms.
Ginger (strong) 5 to 10 ms.
Strophanthus 2 to 5 ms.

Toxins are five in number. They are exotoxins of bacteria obtained from sterile filtrate of the culture.

Toxinum	Preparations	Dose
Diphthericum Calefactum (Schick Control)	Schick test toxin heated to a temperature not less than 70° for not less than 5 minutes.	3 ms. by intradermal injection.
Diphthericum Detoxicatum	A sterile filtrate from a culture on, or in, a suitable medium of *Corynebacterium Diphtheriae.*	By intramuscular injection the volume indicated on the label as the dose on 2 to 3 occasions, at intervals of 2 or 4 weeks.
Diphthericum Diagnosticum	Prepared from a culture on nutrient broth of *Corynebacterium Diphtheriae.*	3 ms. by intradermal injection.
Staphylococcicum Detoxicatum	Sterile filtrate of a culture of a toxigenic strain of *Staphylococcus.*	0.05 ml. increased to 1 ml.
Tetanicum Detoxicatum	Sterile filtrate of a culture on a suitable medium of *Clostridium tetani.*	By subcutaneous or intramuscular injection 0.5 to 1 ml. 1st dose : 2nd dose after not less than six weeks, 1 ml.

Trochisci.—Troches or Lozenges are flat solid tablets composed of a basis and one or more active drugs uniformly divided, for the purpose of slowly melting in the mouth. The quantities given are for 1000 lozenges. The B. P. has the following for the preparation of their bases :—

Take 1000 times the quantity of the drug ordered for one lozenge ; dissolve such salts of alkaloids as may be ordered in 20 mils, or a sufficient quantity of distilled water ; mix the solution with 1000 grms. of sucrose and 70 grms. of acacia, both finely powdered. Incorporate 20 mils of tincture of tolu, and any other drugs ordered.

Note :—M=Maceration. P=Percolation. S=Solution

Make into a paste with sufficient distilled water; divide into 1000 equal lozenges, dry at a moderate temperature.

Trochiscus	Ingredients	Strength in each	Action and uses
Acidi Tannici	Tannic acid 30 G.	1/2 gr.	A local astringent
Bismuthi Co.	Bismuthi carb. 150 G., heavy mag. carb. 150 G., calc. carb. 300 G., acacia 70 G., sucrose 1000 G., oil of rose 0.05 ml., water q.s.	2¼ gr. 2¼ gr. 4½ gr.	Antacid
Krameriae	Extract of Krameria 60 G.	1 gr.	Astringent
Krameriae et Cocainae	Extract of krameria 60 G., cocaine hydrochloride 3 G.	1 gr. 1/20 gr.	Astringent and anaesthetic
Morphinae et Ipecacuanhae	Morphine hydrochlor. 2 G., powdered Ipecac. 6 G.	1/32 gr. 1/10 gr.	Allays cough
Penicillini	Penicillin (cal. salt), sucrose or lactose or both	500 Units	
Phenolis	Liquefied phenol 35.5 ml., acacia 90 G., tragacanth 30 G., citric acid 7 G., carmine 3 G., sucrose 1000 G., water q.s.	1/2 gr.	Antiseptic

Unguenta.—Ointments are semisolid or soft preparations for external application containing some active drugs mixed with a fatty, oily or paraffin basis. Lard, either plain or benzoinated, glycerin, prepared suet, beeswax, etc., either alone or in combination, ointment of wool alcohols, hydrous ointment, emulsifying ointment, form the basis of all B. P. ointments.

There are twenty-five ointments in the B. P. They may be divided into two classes, viz.—(1) General, and (2) Mercurial.

General Ointments

Unguentum	Composition	Strength	Action and uses
Acidi Borici	Boric acid, 10 G.; paraffin ointment 990 G.	1 p.c.	Antiseptic
Acidi Salicylici	Salicylic acid, 20 G.; ointment of wool alcohols, 980 G.	2 p.c.	Antiseptic
Alcoholium Lanae	Wool alcohols, 60; hard paraffin, 240; white or yellow soft paraffin 100; liquid paraffin 600.	6 p.c.	Basis for ointment
Aquosum	Ointment of wool alcohols, 500 G.; distilled water, 500 ml.	50 p.c.	Emollient
Capsici	Capsicum, 25 G.; simple ointment, 95 G.	20 p.c. about.	Rubefacient
Dithranolis	Dithranol, 1 G.; Yellow soft paraffin 999 G.	0.1 p.c.	Antiparasitic
Emulsificans	Emulsifying wax, 30 G.; white soft paraffin 50 G.; liquid paraffin, 20 G.	30 p.c.	Ointment Base
Emulsificans Aquosum	Emulsifying ointment, 300 G.; chlorocresol, 1 G.; distilled water, 699 G.	30 p.c.	Ointment Base
Hamamelidis	Ext. hamamelis liq. 10 ml.; wool fat, 50 G.; yellow soft paraffin, 40 G.	10 p.c.	Astringent
Paraffini	White bees wax 20 G.; hard paraffin, 80 G.; white or yellow soft paraffin, 900 G.	..	Ointment Base
Penicillini	Penicillin (cal. salt), q.s., ointment of wool alcohols, 100 G.	500 Units per G.	Anti-infective
Phenolis	Phenol 30, white beeswax 75, lard 50, hard paraffin 75, white soft paraffin 770.	Not less than 2 p.c. Phenol.	Antiseptic
Simplex	Wool fat 50, hard paraffin 100, white or yellow soft paraffin [illegible]0.	..	Basis for ointment

Unguentum	Composition	Strength	Action and uses
Sulphuris	Sublimed sulphur 1, simple ointment 9.	10 p.c.	Antiparasitic, cures scabies
Zinci Oleatis	Zinc sulphate 30 G., hard soap shavings 90 G., boiling distilled water and white soft paraffin, each q.s.	5.2 p.c. ZnO.	Mild astringent
Zinci Oxidi	Zinc oxide 15, simple ointment 85.	15 p.c.	Mild astringent
Zinci Oxidi Aquosum	Zinc oxide 15, hydrous ointment 85.	15 p.c.	Mild astringent

MERCURIAL OINTMENTS

Unguentum	Composition	Strength	Action and uses
Hydrargyri	Mercury 300, oleated mercury 15, wool fat 430, white beeswax 70, white soft paraffin 185	30 p.c.	Resolvent, antiparasitic
Hydrargyri Ammoniati	Ammoniated mercury 25, simple ointment 975	2.5 p.c.	Antiparasitic Destroys pediculi
Hydrargyri Co.	Mercury ointment 40, yellow beeswax, olive oil, each 24, camphor 12	12 p.c. of Hg.	Absorbent, useful in glandular enlargement, etc.
Hydrargyri Dilutum	Mercury ointment 333.3, simple ointment 666.7.	10 p.c. of Hg.	Do.
Hydrargyri Nitratis Dilutum	Mercuric nitrate ointment 2, yellow soft paraffin 8.	1.34 p.c. of Hg.	Same as above. Invaluable in eczema, tinea tarsi
Hydrargyri Nitratis Forte	Mercury 1 gm., nitric acid 3 mils., lard 4 gms., olive oil 7 gms.	6.7 p.c. of Hg.	A local alterative, astringent and stimulant
Hydrargyri Oleati	Oleated mercury 25, hydrous ointment 75	5 p.c. HgO.	Same as Ung. Hydrarg.
Hydrargyri Subchloridi	Mercurous chloride 20, hydrous ointment 80	20 p.c.	Antisyphilitic, alterative and resolvent

Vaccina Bacterialia. Bacterial Vaccines.—A bacterial vaccine is sterile suspension of micro-organisms or a sterile extract, or derivative, of micro-organisms. Vaccine may be either a simple vaccine prepared from only one species, or a compound vaccine, prepared by mixing two or more simple vaccines made from different species, or varieties, of micro-organisms.

Vaccinum	Composition	Dose
Acnes	20, 100 or 1000 millions of acne bacilli (*Corynbacterium acnes*) in 1 ml.	5 to 1000 millions at intervals of 3 to 10 days
Choleraicum	8000 million cholera vibrios (*Vibrio cholerae*) in 1 ml.	*Prophylactic* : 1st dose, 0.5 ml. ; 2nd dose after 7 to 14 days 1 ml.
Dysentericum (Flexner)	100 millions each of V,W,X,Y,Z, types of Flexner's dysentery bacilli (*Bacllus flexneri*) in 1 ml.	*Prophylactic* : 0.5, and 1 ml. at intervals of 7 to 14 days, 3 doses.
Febris Flavae	A serum-free, aqueous suspension of chick embryo tissue infected with strain of yellow fever virus known as 17D	Not less than 500 LD50 doses, *subcutaneously*
Pertussis	1000 to 10,000 million whooping cough bacilli (*Haemophylus pertussis*) in 1 ml.	*Prophylactic* : 1000 to 20,000 millions on 4 or 5 occasions at intervals of 1 to 7 days. *Therapeutic*: 500 to 10,000 millions at intervals of 1 to 7 days.
Pestis	2000 million (*Pasteurella pestis*) in 1 ml.	0.5 to 1 ml.

Vaccinum	Composition	Dose
Staphylococcicum	100 to 1000 million staphylococci (*Staphylococcus aureus*) in 1 ml.	*Therapeutic* ; 10 to 1000 millions at intervals of 3 to 7 days
Tuberculinum	0.00001 to 0.1 mg. of tubercle bacilli (*Mycobacterium tuberculosis*) in 1 ml.	*Therapeutic* ; 0.000001 to 0.1 mg. at intervals of 3 to 7 days
Typhi Exanthematici	A sterile suspension of typhus rickettsiae which have been killed	0.25 to 1 ml. *subcutaneously*
Typho-paratyphosum	1000 typhoid, 500 paratyphoid A and 500 millions paratyphoid B in 1 ml.	*Prophylactic* ; 1st dose, 0.25 to 0.5 ml. 2nd dose after 7 to 21 days 0.5 to 1 ml.
Vacciniae	A preparation of the vaccinal material obtained from the vesicles produced by inoculation of vaccinia virus on the skin of healthy animals	0.06 ml. (1 min.) by *scarification.*

NON-OFFICIAL OR NON-PHARMACOPOEIAL PREPARATIONS

Ampoulae or ampoules are glass containers intended for injection.

Balnea. Baths.—The immersion of the whole or a part of the body in some liquid or vapour is called a bath. It is said to be general when the whole body is brought under its influence, and local when a part only.

Properly speaking, only medicated baths come under non-official preparations ; but a description of the different kinds of medicated and non-medicated baths will be given here.

A. Cold Bath.—Temperature 35° to 75° F. Average 50° to 60°F. It has a powerful tonic action increasing digestion, metabolism and body weight ; but in order to obtain these effects the bath should not be continued long after the primary reaction has set in. If it is prolonged it may cause secondary depression followed by delayed reaction. In fevers, it abstracts heat and thereby lessens tissue change and prevents complications ; hence it is very useful in hyperpyrexia of **rheumatism, typhus, typhoid,** and **pneumonia.** The bath must be repeated if the temperature rises. There are several ways of using a cold bath. The following are a few examples :—

1. **Cold Affusion.**—In this 5 to 6 gallons of cold water are thrown over the body. It is valuable for resuscitating persons from syncope, narcotic poisoning, convulsions, sunstroke, hysteria, etc.

2. **River Bath.**—Bathing in the river is more invigorating than a full cold bath either in a tub, reservoir, or a tank. It stimulates digestion, gives tone to the system and strengthens muscles, especially if it is accompanied by swimming, or if the current of the water is very strong.

3. **Cold Shower Bath** is an effective tonic, being useful in mania, hysteria, sunstroke, etc. **Needle Bath** is a shower bath thrown in a fine spray.

4. **Cold Sitz-Bath** or **Cold Hip-Bath.**—In this the person sits in a tub with the water up to his hips. The vessels of the cooled surface and intestines first contract and then dilate, especially when friction is applied.

5. **Cold Foot-Bath** tones the system and strengthens the feet, but is to be avoided during the menstrual period.

6. **Cold Wet-Sheet Pack** is done thus :—Spread two blankets over the bed taking care to cover the pillow. Thoroughly wet a bed-sheet and spread it over them. Strip the patient naked and make him lie flat on the sheet. Wrap him up tightly in the sheet and blankets, the ends of the sheet being carefully tucked in on each side and the feet covered. Cover him with two or more blankets, the face being left open. After a short feeling of chilliness the

patient experiences a delightful glow followed by copious perspiration, thereby reducing the temperature, delirium, and irritability. After 1/2 to one hour the packing is removed and the body well rubbed with dry towels.

Instead of cold, tepid or warm water may be substituted. The above description applies to **general packing**, which is usefully employed in **specific fevers**, such as measles, scarlatina, small-pox, etc., to help the development of the rash, or to bring it out if it has receded. To reduce delirium, excitement, and hyperpyrexia, and in mania and insomnia, it is always useful. A local wet pack can be used in pneumonia, chronic diarrhoea, etc. A cold compress round the throat checks the inflammation of acute tonsillitis, whilst a similar compress on the stomach will often check obstinate vomiting.

7. **Cold Douche.**—In this a single stream of water is forcibly directed against a part of the body. Its effects depend mainly upon the size, height, and temperature of the stream, as well as the extent of the surface affected. The douche can be usefully directed against (*a*) *head*, in alcoholic coma and narcotic poisoning ; (*b*) the *spine*, in spermatorrhoea, melancholia, and general debility ; (*c*) *liver* and *spleen*, for chronic congestion and enlargement ; (*d*) *the joints*, for chronic inflammation and stiffness; (*e*) the *perineum*, in which case an **ascending douche** with a rose is used in pruritus ani, haemorrhoids and spermatorrhoea ; (*f*) the *vagina*, in leucorrhoea ; (*g*) *rectum*, in constipation and haemorrhage.

8. **Cold Sponging.**—In this the surface of the body is freely sponged over while the patient is sitting or standing on a shallow tub. It has a tonic and bracing effect.

9. **Ice Bag and Leiter's Coil.**—For local application of cold to the head, chest, or abdomen, an india-rubber bag filled with ice or a closely wound coil of metal tubing through which a continuous stream of water is allowed to flow may be applied.

B. **Warm or Hot Bath.**—It may be either *medicated* or *non-medicated*, general or local. It (*a*) softens the dermis and liquefies the fatty secretions and hence acts as a good **detergent** in many scaly and scabby skin diseases ; (*b*) stimulates local circulation and lessens that of the internal organs, whereby relieves pain of intestinal, biliary, and renal colics ; (*c*) relaxes tissues and relieves muscular spasms in urethral stricture, colic, laryngeal spasm, hernia, infantile convulsions, etc. ; and (*d*) stimulates the secretion of sudoriferous glands, by which many kidney diseases are benefited and uraemia may be averted.

Great care should be taken during and after a hot bath. The patient must be quickly dried, covered, and put in a warm bed. A cup of hot tea, hot milk, or hot water greatly helps diaphoresis.

1. **Tepid Bath.**—Temp. 85° to 95°F. It has a detergent, sedative and antipyretic effect. Useful in pyrexia and restlessness.

2. **Warm Bath.**—Temp. 95°F. to 100°F. Used in fevers, threatening inflammatory affections, etc., as bronchitis, pneumonia.

3. **Hot Bath.**—Temp. 100° to 106°F. Action is the same as above, but more powerful.

4. **Hot Foot-Bath.**—To arrest threatened catarrh, cold in the head, epistaxis, infantile convulsion and to restore menstrual flow stopped by cold.

5. **Hot Sitz-Bath.**—Useful in amenorrhoea, dysmenorrhoea, sudden cessation of menstruation from cold, dysuria, cystitis, etc. The addition of a little mustard helps to re-establish the menstrual flow more quickly.

6. **Hot-water Sponging.**—Sponging the head, temples, and neck with hot water relieves the headache in influenza, catarrh, and other diseases.

C. **Medicated Baths.**—In these, medicinal agents are dissolved in cold or warm water. They may be divided into the following :—

1. **Sea Bath.**—On account of the various saline ingredients held in solution, sea-bathing is especially invigorating and stimulating to the skin. Moreover, the temperature being more or less uniform, sea-bathing is more easily borne by the weak than river-bathing.

2. **Carbonic Acid Bath.**—This is a stimulating saline bath containing sodium chloride 3 p.c., calcium chloride 1 p.c., carbonic acid gas (free) up to 3 grammes to 1 litre. Recommended in heart-disease either functional or organic. The effect of the Nauheim Bath is due to its saline and gaseous constituents.

3. **Acid Bath.**—In this a flannel roller 1 foot broad is soaked in a bath containing diluted nitro-hydrochloric acid 8 ozs. in 1 gallon of water at 98° F., and wrapped twice round the hepatic region, after wringing out the superfluous lotion. It is then completely covered by a piece of oiled silk leaving a little margin. The bath should be renewed morning and evening and worn for days. Useful in hepatic disorders.

4. **Alkaline Bath** is made by dissolving crystallized sodium carbonate (60 grs. to 1 gal.) in water, and is useful in removing scabs and scaly incrustations.

5. **Mustard Bath** (30 to 60 grs. to 1 gallon). A powerful stimulant to the skin, used to quicken the appearance of exanthematous eruptions. The patient should remain in the bath from 5 to 10 minutes.

6. **Bran Bath.**—Bran 4 lbs. are boiled in water 1 gallon, and strained. This liquor is added to water sufficient for a bath. It removes irritation of the skin.

7. **Neem Bath.**—It is prepared by adding the decoction of leaves of *Melia azadirachta* to the ordinary bath. It may be general or local, and is largely employed in India in various skin diseases.

8. **Mineral Water Bath.**—A course of baths in any of the spas has special advantages. The effects of a bath in simple thermal water are similar to those derived from an ordinary warm bath ; but they differ according to the composition of the mineral waters. Thus bathing in and drinking sulphur water are very efficacious in chronic rheumatism, gout, hepatic congestion, etc.

D. **Vapour Bath.**—This may be aqueous or medicated. A **Steam Bath** may be made by boiling water over a spirit-lamp under a cane-bottomed chair, on which the patient sits, enveloped completely, except the head, by one or two blankets. Action and uses are the same as those of hot water bath. The **Russian Bath** consists in exposure of the body to moist vapour at different temperatures. It is said to be risky to persons with weak hearts, and there is certainly more danger of heat stroke than in the **Turkish Bath,** in which only dry air is used. Either of these baths is useful in rheumatism, gout, renal and skin diseases.

E. **Air Bath.—Hot-air bath** may be employed like a steam bath by simply arranging a few electric bulbs connected by wires inside the frame-work which supports the bed clothes, or by passing hot air.

SCALE OF TEMPERATURE OF BATHS (Startin)

Bath	Water	Vapour	Hot Air
Cold	33° to 65°F.		
Cool	65° to 75°F		
Temperate	75° to 85°F		
Tepid	85° to 92°F	90° to 100°F.	96° to 106°F.
Warm	92° to 98°F.	100° to 115°F.	106° to 120°F.
Hot	98° to 112°F.	115° to 140°F.	120° to 170°F.

Bolus.—A bolus is a large pill containing over 10 grains of powdered ingredients. The most convenient plan when a large dose

of a nauseous powder is to be administered, is to give it in a cachet, or wafer paper.

Buginaria.—Bougies are elongated cylindrical preparations containing active drugs mixed with the suppository basis for introduction into the urethral and the nasal cavities. Bougies are made like suppositories but differ from them in shape.

Antrophores are medicated bougies containing a spiral spring wound with fine wire, and coated first with an insoluble layer of white gelatin and then with a diluted mucilage. They may be medicated with cocaine, iodoform, protargol, etc.

Cachets are wafer paper capsules. They consist of two concave or watch-glass shaped halves or discs of wafer paper fixed together at the rims by moisture. Any nauseous or bitter drug can be thus enclosed between the two halves and swallowed without being tasted. Cachets should be dipped in water immediately before swallowing.

Capsules.—A capsule is a gelatin sac enveloping a dose of some nauseous or disagreeable drug.

Carbasa Antiseptica.—**Antiseptic Gauzes** are mulmuls steeped in some antiseptic solution and dried afterwards.

Collutories are throat or mouth paints; as Glycerinum Acidi Borici.

Collyria are eye-lotions or eye-washes. Sometimes they are called eye-drops.

Confectiones.—Confections are soft preparations of drugs, made into a paste with sugar or honey, either to give them a pleasant and agreeable taste or to preserve them. Confectio Sulphuris and Confectio Sennae were official in B.P. 1932.

Elaeosacchara. Aromatic Sugar or Oil Sugar.—These are more common on the Continent than in England, and are made by triturating 9 minims of volatile oils to 1 oz. of sugar. They are used as flavouring agents.

Emplastra.—**Plasters** are made of adhesive substances spread upon a cloth or leather so as to adhere to the skin. They are applied for the purpose of holding medicinal substances in contact with the body, of acting as a protective or support, or of bringing the edges of the wound together. Belladonna and lead plasters were official in B.P. 1932.

Enemata, Enemas, Clysters, Lavements, Rectal Injections.—A liquid preparation introduced into or through the rectum by means of a suitable instrument is called an enema.

If the injection is meant to evacuate the bowels 1 to 2 pints of liquid are injected, the patient lying on his left side; but when it is intended that it should be retained, a small quantity (2 to 4 ozs.) should be used. If it is considered desirable to introduce 3 to 6 pints, the liquid must be slowly thrown up the bowel while the patient is lying first on his left, then on his right side with his pelvis raised, or, if necessary on his knees and elbows, pressing the anus with a towel whenever there are expulsive cramps. This is best done by slowly pouring the fluid into a funnel to which a long gum-elastic tube is attached. It then flows steadily as the result of hydrostatic pressure and is less likely to be ejected. This process is called **Enteroclysis.** It must be borne in mind that the process of injection should be carried on slowly and with occasional pauses, otherwise the enema will be expelled by premature contraction of the intestine. The temperature of the liquid should be 98° F. Cold water is soon rejected.

The following are the chief varieties of enemas with their uses :—

1. **Anthelmintic Enemata** are chiefly used to expel thread-worms, e.g. infusion of quassia or hypertonic saline.

2. **Antispasmodic Enemata.**—For this purpose an injection of

Oil of Turpentine, Asafetida (Tinct. asafetida 6 to 12 p.c. in mucilage of starch), Bromides (Pot. Bromide 1 p. c. with Acetylsalicylic Acid 0.5 p.c., and mucilage tragacanth, in normal saline), etc., is given when the intestine is distended with flatus, or getting cramped.

3. **Astringent Enemata.**—These are used for checking diarrhoea, rectal haemorrhage, and mucus discharge from the rectum and lower bowels.

4. **Emollient Enemata.**—A decoction of starch, linseed, or barley soothes the irritable mucous membrane of the rectum and colon.

5. **Sedative Enemata.**—These are used in painful affections of the rectum, e.g. Tinct. Opii 0.5 to 6 p.c. in mucilage of starch.

6. **Purgative Enemata.**—These are often resorted to when the lower bowels are to be evacuated. Ordinarily, for an adult 1 pint, for a child of four years of age, 4 to 6 ozs., and for an infant 1 oz., are enough. Soap and warm water, thin gruel, and castor oil or olive oil, etc., are often used for this purpose. Glycerin 2 to 4 drs. with an equal amount of warm water injected by means of a suitable syringe, or a glycerin suppository introduced into the rectum, evacuate the bowels speedily.

7. **Nutrient Enemata.**—In case where food cannot be swallowed by the mouth, or retained by the stomach, liquid glucose or dextrose 10 p.c. with normal saline may be given per rectum, not more than 4 oz. at a time. Before the nutrient enema is given the bowel should be washed out each *morning with tepid water.*

Fomenta.—Fomentations consist of flannels, cloths, or sponges wrung out of hot water to which a drug may or may not have been added, for application to the surface of the body.

The proper way to apply fomentations is to take a twofold piece of flannel large enough to cover the affected part. Immerse this folded flannel in a kettle of boiling water or pour boiling water over it in a basin, and lift it by a pair of tongs or a stick, and put it on a wringer—a stout towel or duster with sticks attached to both ends. The water is then squeezed out as much as possible and the flannel applied to the affected part and covered with a large piece of india-rubber sheeting or oiled silk, extending about an inch beyond the flannel. Place over this a thick layer of cotton-wool and bandage. If the full effect of fomentation is desired the flannel should be changed every 20 or 30 minutes. In the case of the feet, hands or fore-arms, dipping them in hot water may do, but its temperature should be maintained by frequent small additions of boiling water.

If it is desired to produce a counter-irritation, oil of turpentine may be sprinkled over the flannel before application. This forms the **turpentine-stupe.** For an anodyne or sedative action, Tinct. Opii may be sprinkled in the same way, or a few poppy-heads or a little opium may be put into the water before boiling.

Dry fomentation is made by filling bags with hot bran, salt, sand, or chamomile flowers. Bottles filled with hot water and covered with flannel bags or old stockings may be used for dry fomentation. A piece of flannel heated over fire and applied also serves the purpose.

Hot Antiseptic Compresses.—These consist of folds of lint or cloth soaked in hot antiseptic lotions and covered with a piece of waterproof, oiled silk, or guttapercha tissue ; as Boric Acid Compress.

Fumigation is a local or general bath of volatilized drugs. Sulphur and mercury are chiefly used for the purpose.

Gargarismata. Gargles.—A gargle is a liquid preparation used for topical action on the mouth, throat, and pharynx. A gargle may be any of the following kinds :—

1. **Stimulant Gargle,** that stimulates the mucous membrane and glands ; as Capsicum (Tinct. Capsicum 2 drs. to Water 8 ozs.), Myrrh, Eucalyptus Gum (120 grs. to 8 ozs.), etc. These gargles

often relieve deafness due to obstruction of the eustachian tube by increased pharyngeal secretion.

2. **Astringent Gargle**, that checks excessive secretion ; as iron salts, zinc salts, alum (12.5 p.c.), tannic acid (30 grs. to 8 ozs.), astringent infusions, etc.

3. **Antiseptic Gargle**, that removes foul secretions and odours; as phenol (5 p.c.), boric acid, potassium permanganate (0.025 p.c.), etc.

4. **Demulcent Gargle**, that removes burning and irritation ; as barley water, linseed tea, isaphgul seed tea, milk, etc.

Gossipia Antiseptica.—Antiseptic Cottons are made by charging absorbent cotton-wool with various antiseptic drugs. This is done by soaking cotton in some saturated antiseptic fluid and afterwards drying it ; as Gossip. Acidi Borici, Gossip. Acidi Salicylici, etc.

Guttae.—Drops are liquid preparations used as drops; as eye-drops, drops for the ear, etc.

Haustus. Draught.—A liquid preparation or mixture when taken in a single dose is called a draught ; as castor oil draught ; chloral hydrate draught, etc.

Insufflations are powders blown into the throat, nostrils, or larynx. Laryngeal insufflation can be managed thus :—Vulcanite tube curved at a suitable angle, having an aperture covered by a slide, through which the medicinal powder is introduced, is carried over the tongue to the laryngeal orifice, and the powder is either blown in by the mouth or by an elastic bulb attached to the end of the tube. This instrument is called "Pulverflator". A quill or a tube half filled with powder and blown by the mouth may do for nostrils and throat.

Jujubes are lozenges made of gum acacia and sugar. They are prepared by boiling to a suitable consistence, gum acacia 16 lbs., sugar 7 lbs., and water 1/2 gal. They are sometimes covered with a coating of crystallised sugar.

Linctus.—Lincture or **Loch** is a thin confection to be slowly swallowed in small doses, so as to act on the throat. The basis of linctus is either treacle, syrup, honey, or any other sweet viscid substance. When powders are the active ingredients they should be made very fine, before admixture with the basis.

Massae.—Masses consist of ingredients mixed together to the consistence of a pill. They were official in the U. S. P.

Mollinum is an ointment prepared with mollin or superfatted soap. It is easily washed off with water forming a lather and leaves the skin fresh and supple. As Mollinum Hydrargyri. Mollin contains 17 p.c. of uncombined fat and 30 p.c. of glycerin.

Nebulae are solutions of drugs in aqueous, oily, alcoholic, or glycerinated media to be sprayed into the throat by the help of a spray-producer ; as Nebula Adrenalinae et Cocainae.

Opodeldocs or **Saponimenta** are preparations having as their basis soap liniment. Medicated opodeldocs are official in Continental Pharmacopoeias.

Pastillus or Pastil is a soft jujube variously medicated, having glyco-gelatin as its basis instead of gum acacia and sugar. These are used like lozenges. As Pastilli Mentholis.

Perles are minute pills.

Pessi.—Pessaries resemble suppositories, but are intended for introduction into the vagina.

Pigments.—Paints are liquid preparations used for application to the throat, skin or other parts. A pigment differs from a collutoire in that the former is used as a paint for any part of the body, whereas the latter is for brushing the throat or mouth only. As Pigmentum Chrysarobini, Pigmentum Iodi Co.

Sprays are liquid preparations intended for application to the upper air passages through an atomizer.

Steatina.—Steatins, Ung. Extensa or Salve Mulls are ointments of a hard consistence spread on muslin, and capable of being folded and cut at pleasure. Mutton or beef suet form their principal basis.

Sticks or Pencils are solid cylindrical rods prepared by fusing drugs and pouring the melted mass into suitable moulds ; as toughened and mitigated caustics. When the melted mass is poured into a conical mould it is called a cone ; as a Menthol Cone.

Styles are thin bougies about 2 inches long for introduction into the lachrymal sac and nasal duct.

Triturationes.—Triturations are solid dilutions. These are intimate mixtures of substances with lactose.

Varnishes are preparations which, when applied to the skin, evaporate and leave a coating. Varnishes are often medicated.

Vina or Wines are weak tinctures prepared with sherry. They were official in B.P. 1914.

Wafer papers are used to wrap round nauseous or bitter powders to disguise their taste. They are made of flour and water, and become limp when moist. Cachets consist of the same material.

PART II

ADMINISTRATION OF DRUGS

How Drugs Act

By the action of a drug on the human organism is understood the interaction between a drug and the blood and the tissues, whereby either the existing functions are altered or certain functions are brought more into prominence which were latent before. Thus, the functions may be increased or diminished, and the drug is then said to *stimulate* or *depress* as the case may be. Sometimes this stimulation has an injurious effect on the tissues and it is then known as *irritation*. A moderate degree of stimulation continued for a long time leads to fatigue or exhaustion of the organs concerned.

Some drugs act more powerfully on certain organs and tissues than others, and this preferential effect is known as the *selective action of the drug*. Thus some drugs primarily act on the plain muscle, others on skeletal muscles, nerves, glands, renal cells, etc. The exact mechanism of this selective action is however yet unknown. It is possible that there may be a special affinity of a chemical nature between the drug and the responding cells. This fact has been taken advantage of in modern treatment and forms the basis of *Chemotherapy*. Substances have been discovered which are supposed to be harmful to the infecting parasites, *i.e. parasitotropic*, and at the same time harmless to the host, *i.e. not organotropic*, *i.e.* the drug should have a wide margin of safety. The conception of chemotherapy is, however, at its best, a speculation, and most of the chemotherapeutic agents act by definite pharmacological action on the cells of the host.

A drug may affect the body *directly*, *i.e.* when it comes in contact with a particular organ and produces its effects on that organ before it is absorbed or enters the circulation. This *local action* may be one of irritation or may be protective, *i.e.* protects the surface from irritation. Some may have only a local action because they are not absorbed from the stomach or intestine, *e.g.* bismuth and kaolin. This action is also known as the *topical action*. Many drugs produce changes on other organs of the body after absorption and this action is known as the *systemic effect*. The action of digitalis on the circulation or kidneys is the systemic effect of the drug after absorption. This is also called *indirect* or *remote action* of the drug. Thus

the local action of aconite on the tongue is tingling and numbness, and its indirect or remote action on the heart is slowing of the rate due to stimulation of the vagal centre.

By *primary action* is meant the effect that a drug produces in its unaltered state. When a drug forms a different compound in the body which produces the physiological effects, it is known as the *secondary action* of the drug. Potassium and sodium citrates and potassium acetate though not alkaline in reaction render the urine alkaline by being converted into bicarbonates in the blood and excreted as such.

It is not always very easy to explain exactly how the different drugs produce their pharmacological effects on the system. Since the processes of life are governed by the chemical and physical changes in the constituents of the cells, it is possible that the different drugs produce their effect either (a) by acting on the surface of the cell, (b) by penetrating into the cell, or (c) by the action on enzymes. Drugs acting on the cell surface however, will often produce their ultimate effects by involving an enzyme system. Enzymes act as true catalysts and markedly accelerate the rate of various chemical reactions. Thus certain vitamins play some important role in the oxidation-reduction processes through enzymes. Riboflavin, for instance, enters into the formation of Warburg's yellow enzyme along with a protein and phosphoric acid and is distributed throughout the tissues (*see* Vitamin). This enzyme plays an important role in the oxidation process of tissues in association with other enzymes. Many enzymes, on the other hand, are concerned in the destruction and neutralisation, e.g., choline esterase, amine oxidase, etc. It will be seen, when discussing drugs acting on the autonomic nervous system, that drugs while stimulating the different nerve endings act by liberating chemical substances which transform a nervous stimulus into a chemical reaction; for instance, stimulation of the parasympathetic acts by production of *acetylcholine* and that of the sympathetic by the formation of *adrenaline-like* substance. Some drugs act in a purely *mechanical* way, while others affect the various cells of the body by causing changes in the physical phenomena, such as *surface tension*, *osmosis*, etc., and modify the particular function of the cells. Meyer and Overton explain the action of another group of drugs, *viz.*, the narcotics, as being due to their solubility in lipoids. They argue that in order that a drug may produce any physiological effect it must first get into the cell, and other things being equal, one would expect a quicker and more powerful effect from a lipoid soluble substance than from one that is not thus soluble. While discussing narcotics it

will be seen that there are many objections to this theory, and that the action of all narcotics cannot be explained on the theory of lipoid solubility. While the activity of another group of drugs depends upon their adsorptive power owing to the colloidal nature of the cell protoplasm. This is how the bactericidal action of mercury (*see* Mercury), and adsorption of toxins by kaolin are explained.

Substrate Competition.—While describing sulphonamides it will be seen that these drugs offer competition with *p*-aminobenzoic acid for some enzyme-receptor in the bacterial cell, the latter being essential for the metabolic requirements of these bacteria. Three things are necessary for this reaction, *viz.*, a substrate, a competitor and a receptor (enzyme). Dimercaprol (a dithiol) having greater affinity for arsenic than the tissue thiols offers competition with tissue cell (enzyme receptor containing -SH group) and thus prevents the inhibition of enzymes by arsenic. Similarly, eserine and ephedrine produce their effect by competing with acetylcholine and adrenaline respectively, the former for the enzyme choline esterase and the latter for amine oxidase. This conception of substrate competition explains the mode of action of many newly introduced drugs.

The Chemical Composition and Constitution and the Physiological Action of a Drug

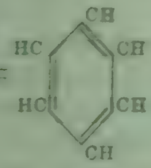
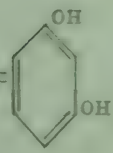
The physiological action of a drug very often depends upon its chemical constitution as will be evident from the following :—

(*a*) *The molecular arrangement in a compound sometimes determines the action of a drug.* Thus isomerides have the same chemical composition and the same percentage of weight, but differ in properties, on account of their different molecular arrangements. Resorcin and pyrocatechin are isomers $C_6H_4(OH)_2$. The former is sweet, the latter is bitter.

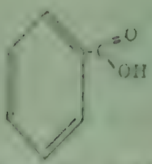
(*b*) *It is possible to modify the physiological action of a drug by artificially modifying its chemical constitution.* Fraser, Crum Brown and others have shown that by introducing a *methyl radicle* into the molecules of strychnine, brucine and thebaine, new compounds are formed, which instead of acting as convulsants, are paralysers of the peripheral terminations of the motor nerves.

Similarly benzol, C_6H_6, the mother substance of the coal-tar series has a low toxicity, because it cannot react with protoplasm. It becomes toxic by replacing part of the H atoms with other groups, specially by OH forming phenol, or by COOH, or by both. The OH radicle is the

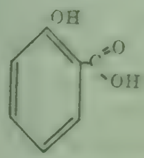
most active ; the antiseptic and toxic action varying with the number of OH group.

Thus benzol=  phenol=  ; resorcin= 

The introduction of COOH group alone, *i.e.* benzoic acid, does not render the substance more active. But both OH and COOH, *i.e.* salicylic acid, results in a compound which is less toxic and less antiseptic than phenol but has a peculiar antirheumatic property.

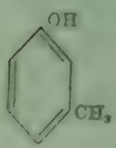


Benzoic Acid

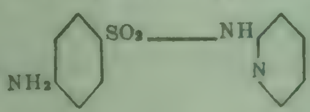


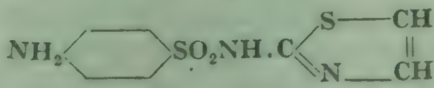
Salicylic Acid

The substitution of an H of C_6H_5 in phenols by alkyls=cresol leads to an increase of the antiseptic power, and diminishes at the same time the toxicity to tissues.



Cresol

Take another example, *viz.*, sulphanilamide, which is para-amino-benzene-sulphonamide = . By substitution of sulphonamide group with pyridine molecule, sulphapyridine is formed=  which has a special action on *pneumococcus*. Similarly by adding thiazole nucleus, sulphathiazole is formed having a special action on *staphylococcus*.



The Action of a Drug and its Power of Dissociation into Ions

Soluble inorganic salts in the body produce their action either by dissociation into ions and exerting their own chemical action, *i. e. ion action*, or display an action due purely to physical changes, *i. e. salt action*. When we consider the action of a powerful drug like strychnine, we find that its various salts produce the same effect which the acid radicle (sulphate, nitrate, etc.) does not modify. This is not however the case with less powerful bodies, *e. g.*

sodium ; here the acid radicle with which it is combined greatly modifies its action, as is observed in the different effects resulting from the administration of $NaCl$ and Na_2SO_4.

To appreciate these differences of action it is essential to understand the *ionic theory*. All substances are divided into two groups, *electrolytes* and *non-electrolytes*. An electrolyte is a substance which is capable of being decomposed by the electric current, as sodium chloride, potassium bromide, etc. The theory assumes that certain substances such as inorganic acids, salts and bases in solutions undergo partial decomposition into their constituent elements or radicles called *ions*. These ions carry definite charges of electricity. Thus sodium chloride, if dissolved in water, exists in part commingled, but not chemically bound sodium *kations* and chlorine *anions*.

$$\underset{\text{(Electrolyte)}}{NaCl} \quad = \quad \underset{+\text{ ion or kation}}{Na} \quad + \quad \underset{-\text{ion or anion}}{Cl}$$

A non-electrolyte is a substance which cannot be further decomposed without losing its chemical identity. In ionic dissociation when the solvent is evaporated the salt is obtained in the same state as before solution ; in chemical decomposition however the evaporation of the solvent will not reunite the separate ingredients.

The importance of this theory to pharmacology is that ordinarily it is the ions of the salts and not the whole molecule which give rise to pharmacological action. For instance, when an ionisable substance is introduced into the blood it has a threefold effect on the functions of the body, *viz.*—

(*a*) that due to the influence of its kation ;
(*b*) that due to the influence of its anion ; and
(*c*) pure salt action.

Sometimes the basic and sometimes the acid ion produces the chief effect, and when neither ions are potent we get the typical salt action. When the two ions are of approximately the same potency we have the combined effects of both ions. The following examples will serve to illustrate :—

$NaCl$=typical salt action.

Na_2SO_4=action of acid ion predominates, and acts as a purgative.

$FeSO_4$=astringent and haematinic, action of basic ion predominates.

$MgSO_4$=action of both ions are equally effective, therefore although the sulphate ion is common with Na_2SO_4 it acts as a more powerful purgative because of the Mg-ion.

Drugs that are not dissociated in the tissues act as molecules and not as ions. This important factor should

be remembered to avoid confusion. Thus potassium cyanide is a poison because CN-ion is dissociable, while in potassium ferrocyanide the CN-ion is not dissociable and therefore this salt is not a poison. Again inorganic arsenic compounds are poisonous whereas cacodylic acid has not the same toxicity because it does not ionise.

It follows that the action of certain drugs depends not only on the amount of dissociation which they undergo but also on the relative absorptive power of the dissociated ions and on the rate of excretion. Scale preparations of iron which do not dissociate are not astringents and do not impair digestion. Mg-ion being absorbed with difficulty and excreted rapidly, its specific effects are not observed when administered by the mouth, although given parenterally it has a profound depressing effect on the central nervous system. The disinfecting power of mercurials varies with the amount of dissociation which the different salts undergo and not on the quantity of mercury in solution. Finally, potassium salts given by the mouth produce no toxic effect because their rate of excretion exceeds that of absorption.

The Reaction of Body Tissues and Body Fluids and the Action of Drugs

By the term reaction of a solution is meant the degree of acidity or alkalinity. The acidity and alkalinity of tissues depend upon the dissociation of H and OH ions, and the degree of acidity of any solution depends upon the relative amounts of free hydrogen ions (H) and free hydroxyl ions (OH) which it contains. When both ions are balanced the solution is neutral. Chemically pure water is neutral and when it dissociates it yields equal amounts of H and OH ions. At 22 C. in ten million litres of pure water there exists in the ionic state 1 grm. of H and 1 grm. equivalent of OH ions. The concentration of hydrogen ions (cH) is therefore 10^{-7} and the concentration of hydroxyl ions (cOH) is 10.

The reactions of the tissues and fluids within the body proper are normally neutral, inclining a trifle towards alkalinity, *i.e.* pH= about 7.1 to 7.8 ; the gastric juice and the urine in higher animals are the only exceptions. The pH of gastric juice is 0.9 to 1.6 ; urine, 6.0 ; cow's milk, 6.7 ; human milk, 7.1 ; saliva, 6.9 ; pancreatic juice, 8.3 ; etc. Living cells are dependent upon the maintenance of a strictly limited H-ion concentration in their environment for the normal performance of their functions.

The normal blood has a pH range of from 7.3 to 7.5 ; and life is incompatible when the pH of the blood is below 7.0 or above 7.8. While the pH of different excretions varies between wide limits, the maintenance of the pH at its normal level in the blood and tissues is very important. This is regulated by a fine adjustment of different mechanisms (*see* Acidosis and Alkalosis). The carbonates and the alkaline phosphates of the blood and tissues form the alkaline reserve, while the carbonic acid and acid phosphates, the acid reserve. These act as "buffers" and tend to neutralise any attempt to change the actual reaction.

The importance of the knowledge of pH of the different tissues of the body to the pharmacologist is great. Action of drugs which are supposed to have a selective affinity for certain organs or tissues

may depend upon their pH reaction. Thus Acton has shown that at pH of 8, quinine kills paramoecium at a dilution of 1 in 10,000; while a concentration of 1 in 100,000 is necessary at pH of 7. Dale has shown that emetine in large doses failed to cure dysentery, in kittens, produced by strains from man, while these men were cured by a course of emetine. It is possible that the pH of the human gut is responsible for the effect of emetine. In fact emetine acts ten times more powerfully, if the acidity of the gut, which has a pH of about 6.2 in amoebic dysentery be reduced or rendered alkaline to a pH of 8. It is therefore argued that besides the drug and the infective organism (*E. histolytica*) other factors have to be considered in the cure of amoebic dysentery, and this missing factor is supplied by the host as the result of interaction between emetine and tissues. It has been found that a dilution of emetine hydrochloride 1 in 5,000,000 is lethal to *E. hystolytica* in *vitro* within four days with a pH of 6.4, while its potency is considerably reduced with a greater acidity. Mercurial diuretics act better when partial acidosis is produced by the use of ammonium chloride. Similarly production of acidosis helps absorption of ionisable calcium. It is clear, therefore, that the action of drugs in certain instances is modified or intensified by the pH of the particular organ or tissues over which they produce the main effect.

CHANNELS FOR ADMINISTRATION OF DRUGS

The following are the various channels through which drugs can be introduced into the system either for their local action or for systemic effects after absorption :—

1. **The digestive tract** is the most important and the ordinarily selected route.

(*a*) *The Mouth.*—We administer drugs by this route either for their absorption by the alimentary tract, or for their local action. Sometimes drugs produce systemic effect through absorption by the mucous membrane of the mouth. Nitroglycerin is often used by this route, and is more effective than when swallowed, because it avoids the portal circulation. *Sublingual* administration of adrenaline is sometimes adopted to avoid decomposition of the drug in the stomach. For local action we use gargles, paints, pastilles, lozenges, etc.

(*b*) *The pharynx* is reached by pigments, pastilles, sprays, insufflations, lozenges, jujubes.

(*c*) *The Stomach and Intestine.*—Drugs are administered by this route either for their local action on the stomach and intestine, for reflex effect from the stomach before absorption, or for systemic effect after absorption. Absorption of drugs from the stomach is relatively small and it does not really occur till the drug has reached the small intestine. For local effect on the stomach digestive ferments, direct emetics, or gastric sedatives are generally used. Purgatives are used for their effect on the intestine and these unfold their action on reaching the gut. Sometimes drugs are administered for action on the intestine and not intended to be dissolved or decomposed in the

stomach. Such drugs are administered in keratin coated or salol varnished pills.

Some drugs are so altered or decomposed during their sojourn in the stomach and intestine that oral administration of such drugs is not followed by any pharmacological effect, while others are too irritant to be used by this route. These are adrenaline, antitoxins, arsphenamine, emetine, etc.

But the greatest use of drugs by this route is for their systemic effect after absorption. The absorption of a drug is influenced by (i) its *solubility*, and (ii) the *conditions under which it is administered*. Thus, a pill takes a longer time to be absorbed than a mixture. Again, salines are more rapidly absorbed than metallic salts or alkaloids. A drug acts more rapidly on an empty stomach than on a full one. On an empty stomach with a healthy mucous membrane crystalloids in solution pass readily through the vessel walls. Colloids on the other hand require to be digested and emulsified before they can be taken up by the blood-vessels and the lacteals. Mixtures, pills, powders, emulsions, etc., are administered by this route.

(*d*) *The Rectum.*—Drugs are sometimes administered by this channel either for action after absorption, or for their local action on the bowel, *e.g.* suppositories, enemas, etc. This route is used to avoid the action of a drug on the stomach and intestine, and since it has a good absorbing surface with its vascularity and venous plexuses, many soluble substances produce their effect more quickly and without passing through the liver where they are likely to be destroyed. Certain anaesthetics and hypnotics are also introduced by this route, *e.g.* ether, paraldehyde, bromethol, etc. ; nutrients (*e.g.* glucose) and saline solution are administered per rectum to maintain the strength of the patient, to counteract toxaemia, or to keep up the action of the kidneys.

2. **The respiratory tract** is the next most important route. Drugs are administered by this route either for their local action in the nose or the lungs ; or for reflexly stimulating the heart and respiration ; or for systemic effect after absorption. Inhalation is carried on by the nose and the mouth. For local action we use collunaria, snuffs, bougies, paints, insufflations, sprays and nasal lavage. Sometimes drugs are sprayed into the nose for action after absorption, *e. g.* the use of pituitary extract in the treatment of diabetes insipidus.

Through this channel vapours or atomised drugs rapidly enter the system. Ether, chloroform, and other volatile and gaseous anaesthetics are used to produce general anaesthesia after absorption from the lung surface ; inhalation of CO_2 with oxygen is used to stimulate

the respiratory centre ; and various antiseptics are used for their action on the trachea, bronchi and the lungs for their local effects. *Aerosol therapy* has been utilised for administration of penicillin by inhalation in different respiratory infections. Iodised oil is introduced to visualise the condition of the lungs and the bronchioles under X-rays.

3. **The skin.**—By the following method, we can introduce medicaments into the body through the skin :

(*a*) *Enepidermic.*—In this method drugs are simply kept in contact with the unbroken skin without friction or rubbing. Pastes, plasters, poultices, fomentations, pigments, creams, ointments, etc., are thus applied.

(*b*) *Epidermic, Iatroleptic or Inunction.*—In this method drugs are rubbed into the unbroken skin to promote their passage between the cells of the epidermis. For this purpose the drugs are either dissolved or mixed with oils or fatty substances. Familiar examples are the cod-liver oil inunction in the treatment of rickets, and the use of blue ointment in the treatment of syphilis. The method is best suited for children.

(*c*) *Cataphoresis or Ionic Medication.*—Some salts when in solution split up into their component ions. When a constant electric current is passed through them, the metallic ions and basic radicles are driven away from the positive pole, and the acid radicles are driven away from the negative pole. This is utilised in medicine by soaking a thick pad in the solution of the drug to be used, attaching the negative pole to the pad when one desires to introduce acid radicles to the tissues, the positive pole being on a neutral part. As for instance the use of sodium salicylate for ionisation of salicylic acid. The exact opposite holds good when basic radicles have to be introduced into tissues.

(*d*) *Intradermal* or *intracutaneous* injection is the introduction of substances between the layers of the skin. This is done in certain skin tests, as the Schick test for diphtheria ; or for the production of infiltration anaesthesia.

(*e*) *Inoculation.*—In this the epidermis is punctured or scarified for introduction of medicaments ; as vaccination.

4. **The subcutaneous tissues.**—These are reached by hypodermic or subcutaneous injections, which is effected by a small syringe to which is attached a fine hollow needle. This is generally done on the forearm, arm, thigh, etc., but when a large quantity is used, *e.g.* saline or antitoxins, the loose areolar tissue of the subscapular region or the mammary region is selected. By this method the drug is quickly absorbed by the lymphatics and the blood-vessels, and any possible reaction in the stomach which may des-

troy its effect is avoided. Moreover one knows exactly the quantity of drug introduced into the system. It has however the disadvantage of forming abscess, which may be sterile from irritant drugs, or septic due to infection from faulty technique.

Hypodermoclysis is the introduction of large quantities of fluids into the subcutaneous tissue, as injection of saline or glucose solutions.

When drugs are introduced by channels other than the gastro-intestinal tract it is known as *parenteral administration*. But the term commonly refers to administration of drugs by injection.

5. **The deep tissues.**—By the same instrument drugs can be introduced into the deeper structures, *e.g.* the muscles and nerves. When the injection is given into the muscles it is called *intramuscular injection*, and it is generally given into the gluteal muscle. Intramuscular injections are given when the quantity to be injected is large, or when suspensions of insoluble drugs are used. The object is to form depots for gradual absorption and continued action of a drug. Apart from the precautions necessary for all injections, the possibility of injecting the drug into a vein, or puncturing a nerve, should be kept in mind. Cases are on record where much harm has been done by injecting an irritant drug into a nerve. Familiar examples of intramuscular injections are those of calomel or bismuth in the treatment of syphilis.

6. **The blood-vessels.**—Through these channels, blood and saline fluid are *transfused*, and drugs are administered *intravenously*. It is the most rapid and certain way of bringing drugs into the circulation and tissues, and is generally used when a definite concentration of the drug is required very rapidly. Thus, during an emergency, when immediate action is necessary it is largely used, *e.g.* intravenous injection of saline solution in the treatment of collapse of cholera ; of strophanthin in cardiac failure ; of glucose and insulin in diabetic coma. It is also used for certain drugs which are either decomposed in the digestive tract, or are too irritant to the stomach and subcutaneous tissues. Well-known examples are the uses of antimony preparations in the treatment of kala-azar ; neoarsphenamine in the treatment of syphilis ; and tryparsamide in the treatment of trypanosomiasis. This route is also selected to secure direct action on the infecting organism in the blood stream, *e.g.* the use of quinine in malignant malaria.

The drugs used by this route must be in complete solution and must not react with the proteins of the blood. Unless there be definite indications, this route should be avoided. Injection of foreign substances directly into the blood

alters the equilibrium of the colloids which in itself may cause alarming symptoms by producing fall of blood pressure or even fatal reaction.

Intravenous administration is commonly used for the following purposes :—

(a) *To bring about certain changes in the blood*; either in volume, in reaction or coagulability. Drugs commonly used are saline solution, glucose, sodium bicarbonate, calcium salts, etc.

(b) *In the treatment of bacterial invasion*: *e.g.* iodine, hexamine, mercurochrome, sulphonamides and antitoxic sera.

(c) *As specifics in certain protozoal infections*; organic arsenic compounds, antimony compounds, quinine, etc.

(d) *In cardiac and circulatory failure*: strophanthin, adrenaline, etc.

(e) *To produce general anaesthesia*: *e.g.* hexobarbitone sodium.

(f) *As diagnostic agents*; iodoxyl, indigocarmine, iodophthalein.

(g) *As sclerosing agents in varicose veins*; ethanolamine, quinine urethane, etc.

Contra-indications.—Acids and metallic salts being incompatible with blood should not be used by this route. Moreover irritant substances may produce thrombosis, inflammation or fibrosis of the veins. It should be avoided in greatly debilitated persons, the old, those suffering from high blood pressure, and who are subject to anaphylactic shock.

7. **The serous cavities.**—These are specially useful when the local action of the drug is required.

(a) *The pleura.*—In empyema penicillin 30,000 to 50,000 units in 30 to 50 mils of saline solution is injected with aspiration of the pus.

(b) *The Peritoneum.*—An injection of saline solution has been advocated in conditions of collapse. The peritoneum may be washed out with antiseptic fluids.

(c) *The Tunica Vaginalis.*—Solutions of iodine, liquefied phenol, or sodium morrhuate are sometimes injected to produce an adhesive inflammation in hydrocele.

8. **The conjunctivae and lachrymal ducts.**—Mydriatics, myotics, and drugs for local action on the conjunctivae and lachrymal ducts are applied either as collyria, ointments or powders.

9. **The ear** is reached by drops, insufflations, etc.

10. **The bladder and urethra** by injections and bougies.

11. **The vagina and uterus** by douches, injections, pigments, pessaries, medicated cottons, etc.

12. **Superior longitudinal sinus** is often punctured to introduce drugs in cases of infants when other veins are not accessible. This corresponds to intravenous injection.

13. **Intraspinal injection** through lumbar puncture is done for the treatment of cerebro-spinal meningitis with antimeningococcal serum, for the production of spinal anaesthesia, or for the introduction of magnesium sulphate or antitetanic serum in the treatment of tetanus.

Diffusible substances are readily absorbed from the subarachnoid space.

14. **Intraventricular injection** is done after trephining the skull, in cases where the ventricles are to be reached. In infants under 18 months this can be reached through the anterior fontanelle.

15. **Intracardiac injection** is resorted to in case of sudden stoppage of an otherwise healthy heart. The best example is the intracardiac injection of adrenaline in drowning, carbon monoxide poisoning, etc.

FACTORS MODIFYING THE ACTION OF DRUGS

Many factors modify the action of a drug. Therefore having selected a drug and the route through which it is intended to be administered, it is necessary that the student should recognise the different factors which modify the action of a drug.

The word "dose", as ordinarily understood, means the quantity of a drug which is necessary to produce a certain pharmacological action either at once or after repetition. By a *maximum dose* is understood the largest quantity which may be given to an adult without producing evil effects ; and by a *minimum dose*, the lowest quantity which is necessary to obtain a physiological action. The B.P. doses represent only average ordinary doses for an adult.

The student should bear in mind that the action of a drug varies with different doses. Thus, tartarated antimony is a diaphoretic in $\frac{1}{32}$ to $\frac{1}{8}$ gr. and an emetic in $\frac{1}{2}$ to 1 gr. doses ; ipecacuanha powder is an expectorant in $\frac{1}{2}$ to 2 grs. and emetic in 15 to 30 grs. Though the B.P. doses are meant as a general guide, yet the practitioner can reduce the minimum and exceed the maximum limits of the pharmacopoeial doses.

Other factors which modify the action of a drug or require consideration in regulating the dose are :—

1. Age.—The dosage varies considerably with the age. By *adult dose* is meant the dose for a person between 20 and 60 years of age. Children should get a fractional part of the adult dose. A practical method of calculating the children's doses under 12 years is given by Young. *The rule is to divide the age in years by the age in years plus* 12 ; *the resulting quotient is the proper fraction of an adult dose.*

Thus the dose

for a child of 1 year, will be $\frac{1}{1+12} = \frac{1}{13}$ of an adult dose

" 4 years " $\frac{4}{4+12} = \frac{1}{4}$ "

Cowling's Rule.—Adult dose $\times \frac{\text{age next birth day}}{24}$

The dose for a child 3 years old will be 4/24 or 1/6th of adult dose.

Dilling's formula is $\frac{\text{age}}{20}$ when calculating with metric weights.

From 12 to 16 years, 1/2 to 2/3, and from 17 to 20, 2/3 to 4/5, are the proportions. Over 60 years, the dosage should again be reduced slightly. For hypodermic medication, the dose is one-half of what is given by the mouth, and for rectal medication, it is the normal dose plus one-fourth, except in the case of strychnine, which should be exhibited in smaller quantities than when given by the mouth.

2. **Sex.**—Women, as a rule being more delicate than men, cannot bear full adult doses. The menstrual period should also be taken into consideration, and strong purgatives should be avoided during this period and pregnancy, or used with care and judgment because of their tendency to cause pelvic congestion which may lead to either severe haemorrhage or miscarriage. For the same reason drugs acting on the uterus should also be used with caution. Many drugs are excreted with milk and this should be remembered when treating nursing mothers. While others pass from the mother to the foetus, and drugs which may not have any effect on the mother may produce a more serious effect on the child.

3. **Size and Body Weight.**—The quantity which is required to produce a certain physiological effect in a strong, healthy and stout person of more than average size and weight, is not necessary to produce the same action on a thin and weak individual.

4. **Idiosyncrasy.**—Individual susceptibility to the action of a particular drug or drugs has long been recognised ; and the unusual or peculiar reaction to a drug is known as *idiosyncrasy*. This may be either too much action, too little action, or an abnormal action not ordinarily observed. Thus we often come across patients who cannot take a small dose of potassium iodide without coryza, though ordinarily many can take it in large doses without inconvenience. Others again are salivated by quite small doses of mercury.

Although one form of idiosyncrasy is shown by increased action of a drug, instances are also common when a drug fails to produce any effect even in comparatively large doses. This form of idiosyncrasy is known as **tolerance**, and when this tolerance exists from birth it is called **congenital** or **natural tolerance.**

Again certain drugs fail to produce the same effects with the same dose when continued for a lengthened period. This is often found with opium. The dose requires to be increased after some time to get the full or the original effects of the drug. This gradual loss of activity is due to **acquired tolerance**. Sometimes the person taking it

becomes so addicted to its use that he actually craves for or indulges in it, to the detriment of his health. This craving for the particular drug is called a **habit** ; and the drug is known as habit forming drug. Persons may contract alcohol habit, heroin habit, cocaine habit, etc.

The toleration is possibly due to (*a*) rapid elimination (atropine in cats) ; (*b*) diminished absorption (arsenic) ; (*c*) destruction of the poison (morphine) ; (*d*) formation of some antitoxin ; or (*e*) the capacity of the body to fix the poison in some non-toxic form.

Although the term tolerance is used with regard to certain drugs, it is also used now-a-days to denote the peculiar form of partial immunity that is developed in certain protozoal diseases like malaria. As a result of repeated infection and reinfection a condition is established in which the host is able to live a more or less healthy life and to offer some resistance to reinfection while still harbouring the parasites in small number. This type of infection immunity is also known as *premunition.*

Racial idiosyncrasy is often noticed and different species of animals vary in their reaction to different drugs. Thus rodents are immune to the action of emetics ; atropine does not quicken the heart in rabbits, etc. It is possible that the failure to react to atropine is due to its destruction in the blood or to the fact that the vagus is not active in rabbits.

Allergy or hypersensibility is also a type of idiosyncrasy and applies both to drugs and food. Although allied to anaphylaxis the reaction does not usually desensitise. It often runs in families and is manifested by the appearance of urticarial rash, oedema, spasm of smooth muscles, etc. The cause of allergic reaction is not clearly understood, although deficiency of calcium in the tissues renders the whole autonomic nervous system susceptible to the action of certain drugs.

Drug fastness or resistance.—It has been observed that pathogenic organisms often acquire tolerance to drugs when administered to the host. Thus gonococcus may acquire tolerance to sulphonamides. Tubercle bacilli often become resistant to streptomycin. This phenomonon is called *drug fastness or drug resistance.*

5. **Rate of Absorption and Clearance.**—The action of a drug depends upon the concentration in the tissue fluids around the organ on which it produces its effects. It follows therefore that when a drug is administered its effects will depened upon the rapidity of absorption and clearance. Administered intravenously a drug acts most quickly than when given by other routes. In most cases however the intramuscular or subcutaneous injections produce quicker effect than when given by the oral route where the action depends upon the rate of absorption and this is influenced by many factors. The action of a drug

and the duration of its effect therefore depend upon rate of excretion, fixation by the tissues, detoxication by oxidation or reduction or formation of some inert body. Drugs which are rapidly absorbed and rapidly excreted should be administered more frequently to maintain a uniform concentration in the blood. To this class may be mentioned the salicylates, penicillin and the sulphonamide group of drugs.

The chief channel of excretion is the kidney, but the rate of excretion of different drugs by this channel is variable, and drugs which are excreted slowly tend to accumulate in the system and may produce toxic symptoms. Although the kidney forms the chief channel of excretion, many drugs, notably the metals, etc., are eliminated by the faeces.

The drugs may be excreted unchanged or may be altered and made harmless before excretion. Liver also helps excretion, but is relatively less efficient since many dyes though excreted by the bile are absorbed from the intestine. It is however a very important organ for detoxicating a poison. This detoxication is done by various means, the most common being by synthesis to form inert compounds. The kidneys also share in this action and can pick up, store and excrete dyes, and also help synthesis, e.g. formation of hippuric acid from benzoic acid.

6. **Mental Condition.**—A morbid inclination of the mind towards the action of a particular drug increases the action of the same. Thus, if a patient can be convinced that he will sleep by a certain draught, small doses of a hypnotic may induce sleep. *Temperament* has some influence on doses. A person with a sanguine or nervous temperament requires smaller doses than one with a lymphatic one.

7. **Fasting.**—A drug acts more powerfully on an empty stomach than on a full one. Thus the same quantity of alcohol, which would intoxicate a person if taken on an empty stomach, can be ingested with impunity if taken during or after meals.

8. **Disease.**—Many diseases considerably modify the dosage of medicines. Thus, opium is borne in surprisingly large doses in biliary and renal colics.

9. **Climate.**—It is a well-known fact that alcohol can be consumed in larger quantites in cold countries than in hot climates.

10. **Method of Administration.**—This is also important. Thus many drugs are too irritant to be administered by the mouth or are decomposed in the stomach. Therefore these require to be administered by the parenteral route. Others again are detoxicated in the liver and do not reach the general circulation. Another group of drugs

produce different effects when administered by the parenteral route than when administered by the mouth. Thus magnesium sulphate is a purgative when given by the mouth and acts as a depressant to the central nervous system when given parenterally. Similarly the dose also requires to be modified when administering by different channels.

11. **Time of Administration.**—Vital force is lowest at the early hours of the morning. Consequently, in debilitating diseases, stimulants are more necessary at this time than later on in the day. It is useless to administer even a very large dose of a hypnotic when the person is up and about ; it should be given at bedtime. Cod-liver oil should always be given after food ; given at any other time it may derange digestion. To avoid irritation of the stomach, iron and arsenic should always be given on a full stomach. Drugs intended for their action on the stomach are best given before meals, e. g. bitters, astringents, bismuth, etc. Saline purgatives which act quickly when given on empty stomach are best administered early in the morning. The more slowly acting purgatives like aloes, etc., are given at bedtime. To avoid hypoglycaemia, the dose and time of administration of insulin require to be regulated in relation to the carbohydrate intake.

12. **Accumulation.**—Ordinarily a drug after introduction into the body is either slowly or rapidly excreted. But if we continue to administer it very frequently for a sufficient length of time, *i. e.* so quickly that it cannot be fully eliminated, or the tissues fail to detoxicate it, a time may come when it will accumulate to such an extent as to produce suddenly toxic symptoms. Drugs which produce symptoms of chronic poisoning are also cumulative and the symptoms are the result of cumulative action. It may be caused by the following circumstances :—

(*a*) *Rapid absorption and slow elimination of a drug.*—This is generally observed with most metals which are not only excreted slowly but the tissues cannot destroy or detoxicate them. Well-known examples are mercury and lead.

(*b*) *Slow excretion due to fixation of the drug in the tissues.*—Digitalis is an example of this class. During a course of digitalis treatment, if no precaution is taken, symptoms of poisoning may suddenly develop without any increase of the dose. This is due to the fact that the body destroys or eliminates an equivalent of 1 to 2 mils of the tincture daily. If therefore a patient is treated with 2 to 3 mils of digitalis tincture daily, sufficient amount may accumulate in the body after some time to produce toxic effects. It is therefore necessary that after full digitalisation the *maintenance dose* should not exceed 1 mil daily.

Slow excretion alone will also lead to accumulation. To this class may be cited bromides. If salt intake is restricted, bromide concentration occurs quickly, but generally bromide concentration rises after three weeks of continuous use. 100 mg/100 c.c. of blood may elicit toxic symptoms.

13. **Antagonism and Synergism.**—Several drugs are often prescribed together, the object being either to counteract some unpleasant or undesirable effect of one by the other, or to reinforce the action of the other. The former effect is known as 'antagonism' and the latter as 'synergism' or 'potentiation.' An antagonist may be a drug, or a substance formed in the body. They may act (1) *by chemical combination* with one another, *e.g.* free acids and alkaline carbonates; oxalates and lime salts; (2) *by true antagonism.* Here the drugs have no chemical affinities for, nor do they react with, each other, but produce opposite effects by acting either on (*a*) *the same structures*, as pilocarpine and atropine, the former stimulates the parasympathetic endings while atropine depresses them; or (*b*) the *different structures, e.g.* adrenaline and amyl nitrite; the former constricts the vessels by stimulating the nerve-endings, while the latter dilates the vessels by direct action on the muscles. (See Physiological Incompatibility, page 64). Volatile oils and hyoscyamus are often used with purgatives to prevent griping. Barbiturates antagonise the effect of strychnine so that large doses of the latter can be given after barbiturates without producing convulsion. Similar antagonism is noticed with sulphonamide group of drugs in the presence of pus and para-aminobenzoic acid, when they fail to produce bacteriostatic action.

It has been found that two or more drugs having the same ultimate effect produce greater effect than any of them when used alone. It has been observed that several purgatives given together act better than one even in doses equal to all. As an example may be mentioned Pil. Colocynth. et Hyosy. B. P. which contains colocynth, aloe and ipomoea resin. Other examples of synergism are: combination of bromide and chloral hydrate as a hypnotic; atropine and adrenaline as broncho-dilator, the former acting by depressing the parasympathetic and the latter by stimulating the sympathetic; ephedrine by inhibiting the action of the enzyme which destroys adrenaline intensifies or potentiates the effect of the latter.

Environment :- Ex: [illegible]

INCOMPATIBILITY

A prescription should not contain such ingredients which can counteract one another either physically, chemically, or physiologically, when mixed together. If they do so, they are known as **incompatibles.**

Incompatibility, therefore, may be of the following kinds :—

I. **Physical.**—This is also known as *pharmaceutical*, and occurs when the ingredients are not soluble in water, so as to produce a clear solution ; as oils, insoluble powders, some spirits, resinous tinctures, some extracts, etc., when ordered in a mixture. Oil, when ordered in a mixture, should be emulsified. Resins, resinous tinctures, insoluble powders, etc., require some suspending agents. Certain solids like menthol, camphor, chloral hydrate, thymol and phenazone when mixed form oily liquids.

II. **Chemical.**—Such drugs should not be prescribed as would chemically react on one another, unless such a reaction is desired. Chemical incompatibility can be classified under two heads :—

A. *Homogeneous.*—In this *no visible change of form*, such as the liberation of a gas or formation of a precipitate occurs, though the colour may be changed. Thus, acids and bases are chemically incompatible with each other ; *e.g.* lactic acid with lime water. Again, if the resulting salt is soluble and poisonous, the chemical neutralisation cannot resist the toxic action, as hydrocyanic acid and alkalies, for potassium cyanide is as poisonous as hydrocyanic acid although the alkaline carbonates are not incompatible with hydrocyanic acid.

B. *Heterogeneous.*—In this there is a *a visible change of form*, *i.e.* the production of a gas or a precipitate ; CO_2 is the chief gas liberated in such a reaction, sometimes H_2S. The precipitates or the insoluble compounds form the largest chemical incompatibles. This class can again be subdivided into :—

1. *Intentional.*—Seidlitz powder, all effervescing mixtures are examples of this variety. Vegetable astringents with iron salts, and lead salts with solutions of opium also come under this category.

Unless the incompatibility in the prescription is intentional the dispenser should first consider whether the incompatibility is of such a nature as would endanger the life of the patient, when it should be referred to the prescriber ; if it is not of such a nature the prescription should be dispensed as ordered adopting such method as will give as satisfactory a combination as can be expected under the circumstances.

2. *Avoidable.*—Sometimes however chemical changes occur by mutual combination of the different ingredients in a prescription with the formation of harmful or even a dangerous compound. This form of chemical incompatibility is very difficult to master. A complete knowledge of chemistry and solubility of drugs can only help the student out of this difficulty. The following rule would

greatly minimise his errors :—"*A drug should never be ordered in combination with any of its tests or antidotes.*" Thus, carbonates should not be given with free acids (except HCN) ; acid salts ; basic salts ; double citrates, *e.g.* scale preparations of iron ; halogens ; solution of ammonia, etc.

Alkaloidal salts, with the exception of quinine sulphate, quinine tannate, quinidine sulphate, physostigmine salicylate, ergotoxine ethanosulphonate, emetine and bismuth iodide, and pelletierine tannate, are soluble in water, although the free alkaloids are only sparingly soluble. Therefore alkaloidal salts should not be prescribed with alkaline carbonates or hydroxides, *e. g.* liquor strychnine hydrochloride with aromatic spirit of ammonia, morphine salts with bicarbonates of sodium or potassium, as free alkaloids will be precipitated. Potassium iodide and tannic acid also throw down alkaloidal precipitates, specially if the solution is concentrated. Many fatal accidents have taken place from swallowing the last dose of a mixture containing a poisonous alkaloidal precipitate. Calcium and other metals of alkaline earth are precipitated by sulphates, phosphates and alkalies ; salts of heavy metals are precipitated by alkalies, tannins, albumin and some alkaloids and acacia. Silver and lead are incompatible with chlorides, bromides and iodides ; silver salts are also incompatible with organic substances. Most metals are precipitated by tannic acid and substances containing tannin. Although, to some extent, the alkaloidal incompatibility can be avoided by the addition of hydrochloric acid and alcohol yet it is a safer plan to follow the following practical rule, viz.—"*All poisonous alkaloids as far as possible should be prescribed in simple solution, and not in too concentrated a state.*"

Sometimes explosive combinations result from inattention to grave incompatibility.

III. **Physiological.**—When the pharmacological action of a drug is antagonised by that of another, both drugs are *physiological incompatibles* or *antagonists.* It is presumed that this antagonism takes place either in the blood or in the tissues. We do not know any drug which can fully and completely counteract the action of another on all points, though instances are common where *partial antagonism* takes place. Thus, opium contracts the pupils and depresses the respiratory centre, belladonna dilates the pupils and stimulates the respiratory centre ; hence both of them are partially physiological incompatibles to each other. Pilocarpine increases, while atropine decreases, both salivation and perspiration. (*see* Antagonism, page 62).

EXPLOSIVE COMBINATIONS

Certain drugs, such as chlorates, bichromates, iodates, nitrates, picrates, permanganates, oxide of silver, etc., are rich in *oxygen* or part with it very easily; while others, such as sulphides, iodine, reduced iron, hypophosphites, organic powders, charcoal, camphor, iodide of iron, ammonia salts, essential oils, etc., are *easily oxidisable.* An admixture between any two of these classes will result in an explosive combination. The following are a few typical examples:—

1. A few tablets of potassium chlorate kept in a pocket with a box of safety matches caused explosion.
2. Potassium chlorate with tannic acid, catechu, morphine hydrochloride, or gallic acid mixed as a dry powder may explode.
3. A mixture of liquor ferri perchloride, glycerin and potassium chlorate explodes when warm.
4. Calcium hypophosphite alone, when triturated hard, sometimes causes explosion. Never heat it with glycerin.
5. Potassium permanganate should not be made into a pill with vegetable extracts or combined with glycerin.
6. Oil of turpentine and sulphuric acid, and amber oil and nitric acid are sure to explode violently.
7. Oxide or nitrate of silver with creosote forms a compound which may take fire if it becomes warm.
8. Chromic acid with glycerin, ether, strong alcohol, or organic substances causes an explosive combination.
9. Chloral hydrate and aromatic spirit of ammonia in a mixture may liberate so much chloroform as to explode.
10. Bismuth subnitrate and sodium bicarbonate given in a mixture liberate CO_2 and may cause an explosion if the bottle is corked before allowing the gas to escape.
11. Liq. iodi and solution of ammonia should not be prescribed together as iodide of nitrogen is formed, which causes explosion.
12. Erythrol tetranitrate is very sensitive to percussion.
13. Chloride of lime triturated with sulphur causes explosion.

POISONOUS COMBINATIONS

1. Potassium chlorate and potassium iodide in solution do not react in ordinary temperatures but in the body produce a poisonous product, probably iodate of potassium.
2. Potassium chlorate given with syrup of ferrous iodide liberates free iodine in the stomach and causes severe gastric irritation.
3. Hydrocyanic acid dilute with metallic hydrates, carbonates, subnitrates, or subchlorides forms cyanides of metals which are more poisonous than the acid.

COMBINATION OF DRUGS

The main object of the prescriber should be to present his patient with an effective and rational prescription free from incompatibles. An admixture of several ill-understood and ill-chosen drugs should be avoided. No drug should be ordered unless the prescriber is sure of the pharmacology of the drugs he is using. Simplicity in combination should be the rule, but it does not follow that one drug only is to be prescribed at a time. An effective combination of judiciously selected drugs is of great value in the treatment of disease. The following are the advantages of a good combination :—

1. *By a combination of various drugs, whose actions bear resemblance with one another, we can augment or intensify certain properties of a drug. See* **Synergism, page 62.**
2. *By a careful admixture of corrigens, we can correct unpleasant and undesirable properties of a drug.*—Thus, ginger is added to Pulv. Rhei Co., Pulv. Jalap. Co., to remove griping. Hydrobromic acid lessens cinchonism.

3. *By a combination of two or more drugs, individually producing entirely different physiological effects, we can sometimes increase the potency of a remedy in a particular direction.*—Thus, by combining mercury with digitalis and squill, we can increase the diuretic properties of the latter drugs.

4. *By mixing such drugs as chemically decompose each other we at times get better results from the resulting products.*—Thus by giving sodium bicarbonate with citric acid, we get the benefit of carbonic acid gas and sodium citrate.

5. *By a combination of such substances as would assist the solubility or absorption of a drug, a more effective remedy can be obtained.*—Thus salicylic acid is almost insoluble in water, but it is rendered soluble by the addition of borax, alkaline carbonates, hydroxides, etc. The absorption by the skin of the alkaloids of belladonna is greatly facilitated if it is combined with fat, glycerin, oil or chloroform.

ART OF PRESCRIBING

WEIGHTS AND MEASURES IN A PRESCRIPTION

The weights and measures of capacity and length to be used in a prescription are those of the Metric System (*see* p. 9). The Imperial system however is still used, and also the scruple, though rarely. Besides, certain signs indicating weights and measures of capacity are also common, which have not been officially recognised. They are :

Gr.=Granum, 1 grain=1/480 of a Troy ounce, or 1/437 of an Avoirdupois ounce.
℈=Scrupulum, 1 scruple=20 grains.
ʒ=Drachma, 1 drachm=3 scruples or 60 grains or 1/8 of a *fluid* ounce, or 60 minims.
℥=Uncia, 1 ounce=1 Troy (480 grs.) or 1 fl oz. (480 minims) or 437.5 grains of water.
M.=Minimum, 1 minim=1/60 part of a drachm or the volume of 0.91146 grain of water.
Gtt.=Gutta, 1 drop, supposed erroneously to represent 1 minim.
O.=Octarius, 1 pint=20 fluid ounce, or 1¼ lbs. of water.
C.=Congius, 1 gallon=8 pints or 10 lbs. of water.

As these symbols are apt to be misleading, the B. P. recommends that prescribers should cease to employ them. Solids should be prescribed in grains (gr.), when Imperial system is used, and ounces (oz.=437.5 grs.) ; and liquids in minims (m.) and fluid ounce (fl. oz.). The quantities should be written in Arabic numerals. The symbol of gramme should be G. and for grain (gr.).

When 'drop' is used it should be measured by means of a tube which delivers in 20 drops 1 G. of distilled water at 15°C.

English Domestic Measures

A tea-spoonful=1 fluid drachm, or a little more.
A dessert-spoonful=2 fluid drachms (about).
A table-spoonful=4 fluid drachms or 1/2 ounce (about).
A wine glassful=2 fluid ounces, or more.
A gill=4 fluid ounces, or more.
A breakfast-cupful=8 fluid ounces, or more.
A glassful=12 fluid ounces, or more.
A tumblerful=15 to 20 fluid ounces.

These are only average measurements, for no cups or spoons are of the same size.

Indian Domestic Measures

MEASURES OF CAPACITY CURRENT IN THE BENGAL PRESIDENCY

A Half-kancha=1/8 chattack or 1/128 seer=2 fl. drachms (about).

A Kancha=1/4 ch. or 1/64 seer=4 fl. drachms, or 218.75 grs. of distilled water.
A Half-chattack=1/8 poa or 1/32 seer=1 fl. ounce (about).
A Chattack=1/4 poa or 1/16 seer=2 fl. ounces (about).
A Poa=1/4 seer=8 fl. ounces (about).
A Half-seer=1/2 seer=16 fl. ounces (about).
A Seer or 64 kancha, or 16 chattacks=32 fl. ounces (about).

Indian Domestic Weights

1 Rupee or 1 tola=180 grains.
1/2 Rupee or 1/2 tola=90 grains.
1/4 Rupee or 1/4 tola=45 grains.
1 Nickel 2 anna=90 grains.
1 Nickel anna=60 grains.

PRESCRIPTION WRITING

A prescription is **simple**, when it contains a basis and a vehicle or excipient with or without a corrective ; and **complex** when it contains several adjuvants and corrigents besides the basis. The construction of a model prescription should be in the following order :—

1. The **superscription**, which consists of the symbol ℞ which originally symbolized the planet Jupiter, but now stands for *recipe* or take thou.

2. The **inscription** or the body of a prescription consisting of the names and quantity of drugs ordered, and contains the *basis*, or the chief ingredient ; the *adjuvant*, to assist the action of the basis ; the *corrigent*, to correct the undesirable effects of other ingredients ; and the *vehicle* or *excipient*, to give the prescription a suitable form.

3. The **subscription**, or the directions to the dispenser, such as *misce, fiat, mist, pilula, etc.*

4. The **signature** (from L. *Signature*—Let it be labelled) or the direction to the patient. This is written either in English or in vernacular.

5. The **prescriber's name or initial** and the **date**. These are put at the bottom. The patient's name is written at the top of the *recipe*.

The following is an example :—

Patient's name :

Superscription :	℞	
Inscription :	Quinin. Sulph.	gr. 10 (*basis*).
	Acid. Hydrochlor. Dil.	ms. 10 (*adjuvant*).
	Syr. Limon.	ms. 60 (*corrigent*).
	Aqua Chlorof.	ad. fl. oz. 1 (*vehicle*).
Subscription :	Fiat mistura, Misce.	
	Mitte tales six.	
Signature :	One ounce thrice a day.	

Date ***Prescriber's Name***

It will be observed that quinine is given with the object of checking malaria, and as the sulphate is insoluble in water, acid. hydrochlor. dil. is used to dissolve it. Chloroform water is used as a diluent and to make the dose a measurable quantity. A vehicle may be of no medicinal value, *e.g.* plain water, or only used to give flavour. Sometimes it has a medicinal value, as when infusions are used. "ad" fl. oz. 1 means that after all the ingredients have been measured the vehicle should be added to make the total quantity one ounce.

In the above prescription the quantities have been given for a single dose and the dispenser is asked to supply six doses. Sometimes, however, instead of depending on the dispenser to calculate the total quantities of each ingredient, the physician makes the mental calculation for the whole amount contained in the prescription.

The above prescription in this case takes the following form :—

Patient's name :

Superscription : ℞		
Inscription :	Quinin. Sulph.	gr. 60 (*Basis*).
	Acid. Hydrochlor. Dil.	ms. 60 (*Adjuvant*).
	Syr. Limon.	ms. 360 (*Corrigent*).
	Aqua Chlorof.	ad. fl. oz. 6 (*Vehicle*).
Subscription :	Fiat mistura. Misce. Put six marks.	
Signature :	One mark three times a day	

Date *Prescriber's Name*

Let us take another example. Supposing we wish to write a sleeping draught for an adult, we first of all think what hypnotic will suit our patient, and decide on chloral hydrate and write accordingly.

℞
Chloralis Hydras, which forms the *basis*

Then we argue that another preparation like potassium bromide will help in its action and will act as an *adjuvant*, we therefore write as

℞
Chloralis Hydras
Potassii Bromidum

We now consider an agreeable corrective and vehicle which would give it a flavour, and therefore add further

Syrupus Aurantii
Aqua Dest.

Having written so far we consider the dose. Here we must be guided by the object for which the prescription is given, and whether the patient should take only one dose or more than one. We order for two doses in case the first dose does not produce the desired effect. The dose of chloral hydrate is 5 to 30 grs. and of potassium bromide is 5 to 20 grs. We decide on giving 15 grs. of each, and for two doses we order 30 grs. of each. Now we add 60 ms. of syrup for each dose and sufficient vehicle to make up the total bulk to 2 ozs. Then we write directions to the dispenser, *i.e.* to mix and make a draught, *viz.*—M. ft. Haust., and the final direction—*Sig.*—one ounce to be taken at bed time to be repeated after two hours if necessary.

The complete prescription will now take the following form :—

Patient's name :

Chloral. Hydras Pot. Brom.	..	aa grs. 30
Syr. Aurant.	..	ms. 120
Aqua Dest.	..	ad. fl. oz. 2
M. ft. Haust.		

Sig.—One ounce at bed time to be repeated if necessary after two hours.

Date *Prescriber's Name*

Sometimes a prescription is written in bulk and the patient is directed to take the required amount from it thus :—

℞

Sod. Sulph.	..	grs. 120
Mag. Sulph.	..	„ 240
Sod. Bicarb.	..	„ 120
Mag. Carb.	..	„ 60
M. ft. Powder		

Sig.—Two teaspoonfuls in half a tumbler of water every morning.

Date : *Prescriber's name*

In writing prescriptions the following points should be observed :—

1. Always begin each line with a capital letter.

2. It is better to write the names of the active ingredients first and then of corrective, etc., and vehicle or excipient last.

3. Use Latin names for the ingredients and for the directions to the dispenser. The directions to the patient may be given in commonly used Latin; but the dispenser must write the directions on the label either in English or in the vernacular of the place.

4. When in doubt always write in English. It is important that the dispenser should understand the meaning of expressions used.

5. Never hand over the prescription without reading it over again.

ELEGANT PRESCRIPTION

Elegance in a prescription should always be aimed at, but it does not follow that the student should prescribe only fancy pills, capsules, tablets and cachets. These are good and useful, but they cannot supply the place of a mixture. The importance of giving a mixture in an inviting and palatable form cannot be over-estimated. We have various flavouring agents. Aromatic syrups, syrup of orange, glucose, lemon, Virginian prune, tolu and ginger are the popular ones. During the hot months, mixtures containing syrups soon decompose, but glycerin and flavouring waters may be substituted for them. Spirit of chloroform, chloroform water and liquid extract of liquorice cover the taste of many bitter and saline mixtures. Rose water, orange-flower water, cinnamon water and anise water are good flavouring vehicles either for mixtures or for lotions. Cinnamon water disguises the odour of castor oil. Syrup of rose, compound tinctures of lavender and cardamoms are used both for flavouring and for colouring purposes. Liniments or ointments can be perfumed by otto of roses, oil of lavender. Nauseous and bitter powders can be given in cachets or pills, the pills may be coated or gilded.

DIRECTIONS TO THE PATIENT

Make it a point to give directions in a definite manner. They should be short, simple and to the point. It is very important to mention the hour of the day when medicines are to be administered. To the student this may appear confusing in the beginning, but the following hints will aid him in this direction :—

1. Mineral acids, as a rule, are given after meals.

2. Alkalies when used to neutralise acid secretion should be given after food, and when prescribed as a systemic alkaliser, should be given between meals.

3. Gastric sedatives, such as dilute hydrocyanic acid, bismuth salts, are best given on empty stomach, as we want their local action.

4. Pepsin, papain, taka-diastase should be given immediately after or along with meals.

5. Dilute hydrochloric acid when prescribed to help intestinal digestion should be given one to two hours after food, so also pancreatin and other pancreatic ferments.

6. Cod-liver oil and its preparations should be administered after and not before food. If given before they spoil the appetite.

7. All preparations of iron, specially the astringent varieties, are to be administered after meals.

8. All stomachics and bitter tonics, such as calumba, chiretta, quassia, are given quarter to half an hour before food.

9. Arsenic is always given after meals, except in a few rare cases, when its local action on the stomach is desired.

10. Potassium permanganate is always given after food.

11. Purgatives should be given either at bed time or early in the morning depending upon the rapidity of their action. Castor oil and salines are best given early in the morning as they take only

a few hours to act. The more slowly acting ones, e.g. bed pills containing aloes, etc., should be given before retiring at night.

12. Emmenagogues should be taken at least one week before menstruation.

13. All diaphoretics act well when the patient is kept warm, and diuretics when cool.

14. Hypnotics, as a rule, should be taken at least half an hour before going to bed ; but sulphonal two or three hours before, as it is absorbed slowly.

15. Morphine should be administered subcutaneously when the patient is in bed.

16. Bromides, when given as a sedative, are to be administered after meals or at bedtime.

PRESCRIPTION FOR CHILDREN

Great tact and caution are required in prescribing for children. The hints given below will greatly help the student in this direction:—

1. The dosage must be in proportion to the age.
2. The bulk of a mixture must be small not exceeding one or at the most two tea-spoonfuls.
3. Medicines must be made as palatable as possible. Children like either sweet or tasteless medicines. They refuse bitters. Quinine ethyl carbonate (euquinine) or aristochin may be used as tasteless substitutes for quinine salts. Quinine should not be dissolved in mineral acids, as its bitterness is intensified.
4. Infants do not refuse either castor oil or cod-liver oil, but older children often reject the former. Cod-liver oil with extract of malt is never refused.
5. Do not order pills for children, give dry drugs in the form of powders mixed with honey, syrup, milk, sweetened water, malt extract, or jam.
6. Children bear belladonna and hyoscyamus in fairly large doses.
7. Arsenic, too, is well borne, some choreic children can take very large doses without harm.
8. A tea-spoonful of castor oil to a new-born babe is not a big dose.
9. Children are *very susceptible to opium.* Opium and its preparations should therefore be used with caution in children's practice. *
10. Plain dill or anise waters make good all-round general vehicles.
11. For round worm, santonin must be given on an empty stomach at night and then followed by a dose of Gregory's powder next morning. It is best given with calomel and sugar followed by a saline if necessary.
12. Children tolerate calomel better than adults and are rarely salivated. Similarly sulphonamides are more tolerated by children.
13. Expectorants are best given in the form of syrups or mixed with a syrup.

* In some part of India infants are habituated to the use of opium. It is given with a view to keep them quiet while their mothers are at work. Many wet nurses secretly administer it to their wards.

PART III

PHARMACOLOGY AND THERAPEUTICS

GROUP I

THE ALKALIES AND METALS OF ALKALINE EARTH

Potassium, Sodium, Ammonium, Lithium, Calcium, Magnesium, Barium

CERTAIN salts of the alkalies—potassium, sodium, ammonium and lithium, and some of the salts of the alkaline earth—magnesium and calcium, are *antacids*, *i. e.* they neutralise excessive acid. The salts of the former, being rapidly absorbed from the alimentary canal, manifest after a local action in the stomach, certain systemic effect, whereas the salts of the latter are absorbed with difficulty and exhibit an active action on the intestinal tract, magnesium being laxative, calcium constipating. Some of the alkaline salts are strong caustics, while others are mild antacids. The former are chiefly the hydroxides of potassium and sodium, and the oxide of calcium. These act by dissolving albumin, extracting water and saponifying fats ; while the others, *viz.*, the carbonates and bicarbonates of potassium, sodium and lithium, and the carbonates and oxides of magnesium and carbonate of calcium act only as antacids. Some are not local antacids, but are converted into carbonates and bicarbonates in the blood and tissues and thus increase the alkalinity of the blood, and are therefore systemic alkalisers. They are the acetates, citrates and tartrates of sodium and potassium.

Barium, though it belongs to the group of metals of the alkaline earth, has none of its properties common with calcium and magnesium, except that it is absorbed with difficulty by the epithelial cells.

Antacids are therefore of two types :

1. *Those of alkaline reaction*, viz., (*a*) the caustic alkalies ; and (*b*) the milder alkalies, the bicarbonates and carbonates.

2. *Those not of alkaline reaction*, viz., the acetates and citrates.

POTASII CHLORIDUM

Potassium Chloride.—In colourless, cubical crystals or quadrangular prisms, or a crystalline powder ; odourless ; taste, saline. *Soluble* in about 3 parts of water.

B. P. Dose.—15 to 30 grs. or 1 to 2 grms.

Enters into.—Inj. Sod. Chlorid. Co. ; Inj. Sod. Lact. Co.

PHARMACOLOGY AND THERAPEUTICS

The body contains about 150 grammes of potassium,

i.e. almost twice that of sodium. Most of this is contained in the cells and least in the tissue fluids. Its concentration in the blood is about 20 mg. per 100 c.c. Potassium is controlled by adrenal cortex and when it is diseased or absent, excretion of potassium falls and it is retained in the body. In fact it has been suggested that the symptoms of adrenal deficiency (Addison's disease) are due to potassium poisoning.

Potassium salts are present in large quantity in both animal and vegetable foods, and although they are absorbed in large amounts very little effects of the potassium ion are observed. In fact about 2 to 3 ounces are daily ingested with the vegetable food without any specific action of potassium ion being elicited, because the salts diffuse very rapidly through the cells and are excreted very quickly. It is only when the salt is given intravenously or subcutaneously that the specific effects of potassium ion are observed. These are characterised by depression of the central nervous system and the heart. When used therapeutically potassium salts produce the effects through the acid radicles and are practically equivalent to the corresponding sodium salts. The systemic effect of potassium ion when administered by the mouth is only possible if the dose is very large and the mucous membrane of the intestine is corroded ; or its excretion is checked by ligation of the kidney vessels ; or when the kidneys are diseased.

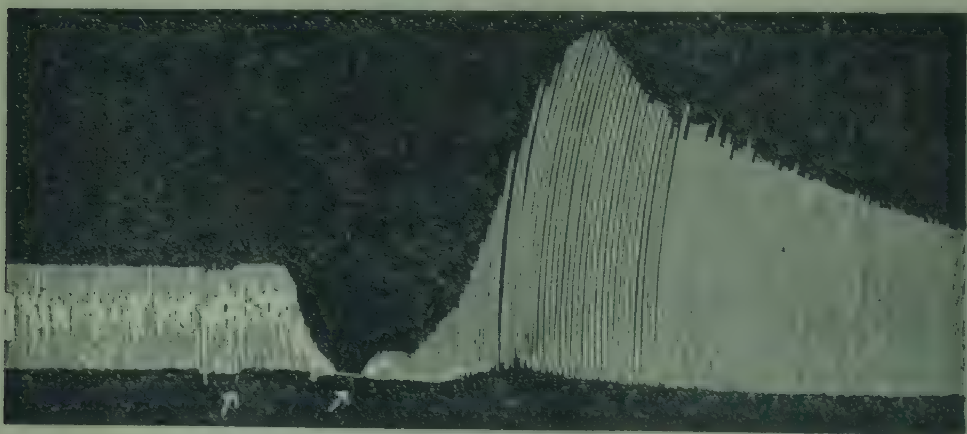


Fig. 1.—Antagonism of Calcium to Potassium

Isolated rabbit's heart perfused with oxygenated Ringer's solution. At the point of 1st arrow a small dose of potassium chloride was added to the Ringer showing depressant effect of potassium on the heart. At 2nd arrow calcium chloride was added. Note effect on the heart.

Potassium ion is necessary for the normal action of the heart. Its absence in perfused fluid will cause the heart to stop in systole which is corrected by the addition of potassium salt. On the other hand if its concentration is too strong the heart will stop in diastole due to

direct depressant action of the potassium ion on the myocardium It is therefore a powerful depressant to the heart which becomes slow and weak. The systole becomes weaker and the heart of a frog stops in diastole. While calcium makes the heart muscle to contract, potassium helps it to relax. Injected intravenously it causes a rapid fall of blood pressure and slowing and weakening of the heart, accompanied by dilatation and heart block, resembling the effects produced by stimulation of the vagus or injection of acetylcholine ; these are not antagonised by atropine. These effects are due to the direct action of the drug on the heart muscle and not to any effect on the vagus mechanism. Reflex vaso-dilatation from the carotid sinus may have some share in the fall of pressure.

Injected into an artery instead of into a vein it causes a sudden rise of blood pressure from peripheral vasoconstriction due to its direct action on the muscles of the vessels.

Potassium plays an important part in the transmission of nerve impulse and is concerned in the functional activity of both the voluntary and autonomic nervous system. It also produces a powerful contraction of the skeletal muscle, and possesses an anti-curarising effect, *i.e.* partially overcomes the transmission block produced by curare at the myoneural junction, but has no action when the transmission is normal. The transmission of impulses at the nerve-endings ceases when plasma potassium falls below 9 to 12 mg. per 100 c. cm. in man causing paralysis. Potassium therefore has been used in the *familial periodic paralysis*, in the form of potassium chloride (5 to 10 grm. by the mouth) which restores the serum potassium level lowered in this disease. Improvement follows its use in *myasthenia gravis* in tea-spoonful doses in milk or water three times a day.

With large and repeated doses the muscular movements in frogs become first weak and then abolished ; and in mammals the effects are characterised by muscular weakness and apathy with rapid and laboured respiration from anaemia of the centre.

Recently the toxic action of potassium ion has been emphasised, particularly in old patients and in those with cardiovascular and renal disease.

POTASSII HYDROXIDUM. (Pot. Hydrox.). KOH. **Syn.**—Caustic Potash ; Potassa Caustica.—Contains not less than 85 p.c. of pure Potassium Hydroxide and not more than 4 p. c. K_2CO_3.

Characters.—Deliquescent, corrosive, strongly alkaline, white sticks or fused masses. *Solubility.*—In 0.95 part of water, and in 3 parts of alcohol (90 p.c.).

Official Preparation

1. **Liquor Potassii Hydroxidi.** *Syn.—Liquor Potassae.*—5 p. c. solution in water. A colourless, odourless, strongly alkaline liquid. **Enters into.**—Liq. Cresol. Sap.

Non-official Preparation

1. **Pasta Potassae et Calcis.** *Syn.— Vienna Paste.*—Caustic potash and quicklime in equal weights. Add alcohol or glycerin q.s. to form a paste.

Sodii Hydroxidum. (Sod. Hydrox.). NaOH. **Syn.**—Caustic Soda. Contains not less than 95 p. c. of Sodium Hydroxide.

Characters.—White sticks, fused masses or scales : dry, hard, brittle, showing crystalline fracture. Deliquescent : strongly alkaline and corrosive. Rapidly absorbs CO_2. *Soluble* in 1 part of water, freely in alcohol (90 p.c.).

Enters into.—Mist. Mag. Hydrox.

Potassii Bicarbonas. (Pot. Bicarb.).—Potassium Bicarbonate. $KHCO_3$.

Characters.—Colourless, transparent, monoclinic prisms, or a white granular powder. Taste, saline, feebly alkaline. *Solubility.*—1 in 4 of water. Almost insoluble in alcohol (90 p.c.).

N. B.—20 parts by weight are neutralised by 14 parts of citric or 15 of tartaric acid.

B. P. Dose.—15 to 30 grs. or 1 to 2 grms.

Enters into.—Syr. Ferr. Phosph. Co.

Sodii Bicarbonas. (Sod. Bicarb.).—Sodium Bicarbonate. $NaHCO_3$.

Characters.—A white powder, or small, opaque, monoclinic crystals, with saline taste. Slightly alkaline. *Soluble* in 11 parts of water.

Twenty grammes neutralise 16.7 grms. of citric acid, or 17.8 grms. of tartaric acid.

B. P. Dose.—15 to 60 grs. or 1 to 4 grms.

Official Preparations

1. **Injectio Sodii Bicarbonatis.**—Ordinarily 5.0 p.c. w/v solution shall be dispensed.
2. **Tabellae Sodii Bicarbonatis Compositae.** *Syn.—Soda Mint Tablets.*—**B. P. Dose.—2 to 6 tablets slowly dissolved in the mouth.**

Sodii Carbonas. (Sod. Carb.). Sodium Carbonate. $Na_2CO_3, 10H_2O$. **Syn.**—Soda or Washing Soda.

Characters.—Transparent, colourless, rhombic crystals. Efflorescent. Taste, strongly alkaline ; odourless. *Soluble* in 2 parts of cold water.

Twenty grammes netralise 9.8 grms. of citric acid, or 10.5 grms. of tartaric acid.

Enters into :—Ferri Carb. Sacch. and Liq. Sodae Chlorinatae Chirurgicalis.

Sodii Carbonas Exsiccatus. (Sod. Carb. Exsic.). Exsiccated Sodium Carbonate. **Syn.**—Sodii Carbonas Monohydratus, U.S.P.

Characters.—A dry, white powder : odourless. Taste, strongly alkaline. Readily *soluble* in water.

Enters into.—Pilula Ferri Carbonatis.

Pharmacology of Caustic Potash, Caustic Soda, Carbonate of Sodium and Bicarbonates of Potassium and Sodium

Externally.—Applied to the skin a concentrated solution of caustic potash or caustic soda acts as a powerful **irritant and caustic.** They have a strong affinity for water and dissolve albumin. The solutions of carbonates are less caustic than the hydroxides. A weak solution of caustic potash or a solution of carbonate will soften the skin, dissolve the oily secretions of the glands and cleanse the surface more thoroughly than plain water. Applied for some time they penetrate deeply and cause irritation and redness. Caustic potash and caustic soda are therefore **irritant, rubefacient and detergent.**

Internally. **Gastro-intestinal tract.**—The hydroxides and the carbonates have an alkaline taste and dissolve the superficial layers of the lining membrane and the mucous

secretions in the mouth. Concentrated solutions may cause deep erosions as on the skin, while very dilute solutions only excite a reflex flow of saliva. In the stomach the hydroxides and the carbonates exert the same corroding effect when given in concentrated solutions ; in dilute solutions they are **mild irritants** and may cause **gastritis.** The bicarbonates produce no such effect on the stomach. They dissolve mucus and neutralise acid, but their effect like all alkalies will vary greatly according to the nature of the stomach contents at the time of administration. Given during the digestive period they have the following definite effects, *viz.*—(*a*) reduce the gastric secretion ; (*b*) neutralise some of the hydrochloric acid ; (*c*) liberate CO_2 gas which acts as a carminative ; and (*d*) inhibit gastric movement and delay the opening of the pyloric sphincter.

It is claimed that given during digestion alkalies diminish acidity temporarily, followed by a rise above normal. Indeed some hold that while alkalies inhibit gastric secretion when given before meals, they increase the secretion when administered during the meals. This is possibly due to the liberation of CO_2, which increases the gastric secretion. Dilute solutions act as mild irritants to the stomach walls and thus improve the circulation, help expulsion of gas and reduce pain and distension much in the same way as any other mild irritants, like the volatile oils.

In the intestine the alkalies by neutralising or diminishing the acidity of the gastric contents have a retarding influence on the pancreatic secretion, which is normally stimulated by the passage of a highly acid fluid from the stomach although the greater alkalinity of the intestinal contents tends to increase the efficiency of the pancreatic juice already secreted. In hyperacidity, however, the alkalies render the contents of the intestine less irritating and thus have a tendency to allay catarrh. Very large doses cause vomiting. Repeated large doses open the bowels ; the bicarbonate of soda sometimes acting as a purgative.

Heart and circulation.—In therapeutic doses given by the mouth these salts are inert. In India, where a vegetable diet is widely used, very large quantity (1½ to 3 oz.) of potassium salts are ingested daily without any effect, because they are excreted so rapidly that we get no specific action of potassium ion on the heart. In practical therapeutics potassium salts may be regarded as equivalent to the corresponding sodium ones, except when they are given by injection.

Respiratory tract.—These salts stimulate the bronchial secretion, and make the mucus less viscid. They are **reflex expectorants** acting through the stomach.

Absorption and Excretion.—All these salts are ab-

sorbed freely from the stomach and are readily excreted by the kidneys. In the presence of the gastric juice the bicarbonate is converted into chloride and absorbed as such, the portion not neutralised is also absorbed thus increasing the total base equivalent to the amount of alkalies ingested. Even if the total amount of alkali ingested be nutralised in the stomach the reserve alkali available is augmented. During elimination the urine is made less acid or even alkaline. But the urine regains its acidity unless the administration is continued when the reaction of the urine may be kept alkaline for a prolonged period. Passing over the mucous membrane of the genito-urinary tract, they either exercise a direct sedative action on it, or by rendering the urine alkaline soothe any irritation that may be present.

Toxic doses of alkalies, or when they are continued for long as in the treatment of gastric ulcer, cause alkalosis giving rise to headache, vomiting, general prostration, and possibly symptoms of tetany due to diminished calcium in the plasma.

Toxicology of the Caustic Alkalies

Persons are not often poisoned by the caustic alkalies, but accidents occasionally happen through their swallowing by mistake either *peariash*, which is a mixture of potassium carbonate and potash, or *soap-lees*, which contains the corresponding sodium salts.

The *symptoms* are a caustic taste in the mouth and burning heat in the throat, the mucous membrane of which becomes swollen, soft and red. This is followed by pain in the stomach, vomiting, sometimes of blood, diarrhoea, feeble pulse, general collapse from shock. On post-mortem examination, the whole mucous membrane from the mouth to the stomach is found red, swollen and excoriated.

Treatment.—Any rapidly acting emetic, or a hypodermic injection of apomorphine. If no emetics are available, give copious draughts of warm water and tickle back of throat with a feather. After vomiting has occurred give (1) **feeble acids** (*e. g.* vinegar, lime-juice, dilute acetic acid or citric acid); (2) **demulcents** (oil, linseed tea, white of egg).

N. B.—Do not wash out the stomach with the stomach-pump as there is danger of damaging the softened mucous membrane.

Therapeutics of Caustic Potash, Caustic Soda, Carbonate of Sodium and Bicarbonates of Potassium and Sodium

Externally.—Caustic potash in the form of the solid stick is occasionally applied to remove growths such as warts or to destroy lupus. Being very deliquescent its action spreads to the surrounding and deeper tissues and it is necessary to protect the tissues by applying blotting paper to absorb moisture. Acetic acid or vinegar diluted should be applied to neutralise the caustic when further action is not required. As it often causes severe caustic action, the application of Vienna Paste is recommended

which is milder and more manageable. Cotton wool soaked in liquor potassae and applied over an ingrowing toe-nail makes it soft enough to be peeled off easily. A solution of the bicarbonate (60 grs. to 1 pt.) allays itching of many skin diseases, and is used as a soothing lotion in dermatitis, urticaria, etc. A weaker lotion softens the crusts and checks the weeping of raw, red eczema. For this purpose a piece of lint soaked in the lotion is applied to the raw surface and then covered with oil silk to check evaporation. Alkalies are useful in insect bites.

Internally.—While alkalies are either indifferent or disturbing to normal digestion, they are of great value in digestive troubles. In dyspepsia where the gastric secretion has become thin and watery, the bicarbonates are given a few minutes before food; and when there is epigastric pain, heart-burn or acid eructations they are best administered after food. In gastric catarrh and chronic gastritis, alkalies dissolve the mucus which by forming an impermeable coating prevents formation of the gastric juice. In these cases lavage of the stomach is of value to clear the stomach of its mucus and prepare it to receive the food. For this purpose the bicarbonate of soda is commonly used (60 grs. to 1 pint of hot water). Given about twenty minutes before food it tends to call forth the "appetite juice" and is often combined with aromatics and bitters.* In cases of **hyperchlorhydria** and **duodenal ulcer** it will relieve the pain if given two hours or more after the meals. Because of the undesirable systemic effects when used in large doses the use of bicarbonate of soda has been replaced by salts of the alkaline earth, like calcium and magnesium, and alum which act not only as antacids but are not absorbed from the stomach and are adsorbents.† Bicarbonate of soda is used in an effervescing form with citric and tartaric acids, and the CO_2 formed acts as a gastric sedative, and is used in vomiting, gastric irritability, etc.

Although alkalies have no direct effect in increasing the secretion of bile they are used in jaundice often with benefit. This they do by relieving the catarrh of the intestine which causes obstruction of the bile duct.

In severe acidosis, such as may be in delayed chloroform poisoning, cyclical vomiting of pregnancy, large doses of bicarbonate of soda are given by the mouth, by the continuous rectal drop method, or intravenously. It is valuable in diabetic coma. The daily dose should be 1

*Sod. Bicarb.	gr.	15	†Sod. Bicarb.	oz.	1/2
Sp. Chlorof.	ms.	15	Mag. Carb.	oz.	1½
Tinct. Nuc. Vom.	ms.	10	Calc. Carb.	oz.	1½
Inf. Gent. Co. ad.	oz.	1	Bism. Carb.	oz.	1/2
Before meals			Mix. Half to one teaspoonful for a dose		

to 1½ oz. freely diluted, and should be continued until the *p*H of the plasma is normal, and if possible until the reserve alkalinity of the plasma has been restored. Large doses have the disadvantage of producing looseness of the bowels. It should be given freely diluted, preferably between meals. When given subcutaneously, the solution containing bicarbonate should not be boiled, as this drives off CO_2 and converts part of the bicarbonate into carbonate which is highly corrosive to the tissues and may produce sloughing. Bicarbonate of soda is added to saline solution for injection in cases of **cholera** (*see* sodium chloride).

Formerly the alkalies were largely used in rheumatism on the idea that they helped excretion of uric acid. Similarly patients suffering from **gout** are treated with alkaline mineral waters. In both these conditions improvement follows but the precise nature of their action is not known and the explanation so far given is not conclusive.

As an antidote to poisoning by caustic acids, the carbonates and the bicarbonates are to be avoided as they form carbonic acid gas and so cause risk of rupture of the stomach. Caustic potash and other alkaline salts may be used in these cases.

Alkalies, especially the bicarbonates, are largely used either alone or with other expectorants to lessen the viscidity of the secretion in bronchitis and bronchial catarrh.* Indeed potassium bicarbonate is a common ingredient in most cough mixtures.

They render urine alkaline in cases of excessive acidity of the urine. Since the *coli* organisms do not grow freely in an alkaline medium, alkalies are largely used in *Bact. coli* infection of the urinary tract, but to be of any use large doses have to be given (120 to 240 grs. of the bicarbonates daily). Large doses of bicarbonates often cause diarrhoea or irritation of the stomach, therefore citrates and acetates are preferred. As they hold more uric acid in solution, they are used in uric acid diathesis and uric acid calculi, often with good results but the urine should be rendered alkaline, or at least neutral. It should however be kept in mind that excessive alkaline urine is liable to cause deposit of phosphates in the bladder and thus may tend to increase the formation of calculus, though not of the same variety.

Bicarbonate of soda is used with other drugs to prevent deposit of insoluble substances and to antagonise undesirable effects. Thus it is combined with salicylates to

*Pot. bicarb.	grs.	15
Tinct. ipecac.	ms.	10
Sp. ammon. aromat.	ms.	20
Syr. tolu	ms.	30
Aqua camph.	ad. fl. oz.	1

prevent acidosis and irritation of the stomach and with sulphonamides to help absorption and to prevent acidosis and renal injury from acetylated compounds.

Large doses of bicarbonate may cause retention of water and produce oedema. This may occur even in healthy persons and is probably analogous to salt oedema. They may also cause *alkalosis* with injury to the kidneys and retention of nitrogenous elements in the blood.

Prescribing hints.—The bicarbonate should be used in preference to the carbonate, and the salts of sodium in preference to potassium. For intravenous medication sodium bicarbonate only is used in 5 p.c. solution. Alkalies are incompatible with acids and acid salts, e.g. bismuth subnitrate, magnesium sulphate, alkaloidal salts and heavy metals.

POTASSII ACETAS
(Pot. Acet.)

Potassium Acetate. CH_3CO_2K.

Characters.—White foliaceous, satiny masses, or granular particles; deliquescent. Taste, sharp, saline, odourless, or with a faint acetous odour. *Solubility.*—2 in 1 of water, 1 in 2 of alcohol (90 p. c.).
B. P. Dose.—15 to 30 grs. or 1 to 2 grms.

Potassii Citras. (Pot. Cit.). Potassium Citrate.—$K_3C_6H_5O_7, H_2O$.

Characters.—White, granular crystals, or a crystalline powder. Odourless; taste, saline. *Solubility.*—1 in 1 of water.
B. P. Dose.—15 to 30 grs. or 1 to 2 grms.

Sodii Citras. (Sod. Cit.). Sodium Citrate.—$C_6H_5O_7Na_3,2H_2O$.

Characters.—White granular crystals, or crystalline powder with a saline taste. No odour. Slightly deliquescent in moist air, efflorescent in dry air. *Soluble* in less than 2 parts of water, insoluble in alcohol (90 p.c.).
B. P. Dose.—15 to 60 grs. or 1 to 4 grms.

OFFICIAL PREPARATIONS

1. **Injectio Sodii Citratis Anticoagulans.**—Sod. Cit. 2.5 p. c. and sod. chlor. 0.9 p. c. Ordinarily it should be used within one month of its preparation.
2. **Injection Sodii Citratis cum Dextroso.**—Sod. cit. and dextrose 3 p.c. each.
3. **Tabellae Sodii Citratis.—B. P. Dose.—15 to 60 grs. or 1 to 4 grms.** When the quantity in each tablet is not mentioned 2 gr. tablet shall be supplied.

PHARMACOLOGY OF ACETATES AND CITRATES OF POTASSIUM AND SODIUM

Internally. **Gastro-intestinal tract.**—Acetates and citrates do not irritate the stomach and are easily borne. Being neutral they are not direct antacids like the carbonates and bicarbonates, but act as *remote antacids.* The citrates are absorbed less rapidly than the acetates.

Blood.—These salts are converted into bicarbonates in the body; and thus exert an alkaline action after absorption. They have therefore the same action after absorption as alkalies, except that they do not act as direct antacids. When mixed with drawn blood the citrate inactivates calcium by forming double salts which do not liberate calcium ion. and produce typical effects of calcium deprivation. In moderate doses (10 to 50 mils of 10 p.c. solution

in man), given intravenously, sodium citrate shortens the coagulation time of the circulating blood. The mechanism of this action is not clear and has been attributed to injury of the blood platelets and to liberation of thromboplastin.

Kidneys.—They are all **diuretics** and render the urine alkaline. Owing to the low threshold value, potassium salts are rapidly excreted by the urine, and other things being equal, they are more efficient diuretics than the corresponding sodium salts which are more liable to be retained in the body. Although the urine becomes alkaline yet the total amount of acids eliminated is increased. They have very slight effect on the flow in health.

Skin.—They are all **diaphoretics,** but the method of this action is obscure.

Therapeutics of Acetates and Citrates of Potassium and Sodium

Gastro-intestinal tract.—Sodium citrate is largely used as an addition to milk (2 to 5 grs. to the ounce) to render the clots less tough and therefore more easy of digestion. The citric acid prevents the ionic action of calcium and the curd consisting of sodium caseinate is much softer than calcium caseinate. Hence citrated milk is largely used in the curd **indigestion of children** and **diarrhoea** of infants. Given in large doses it causes oedema which disappears on witholding of the drug.

Blood.—These salts were formerly used in the treatment of gout and rheumatism. They act like the alkaline carbonates or bicarbonates but do not irritate the stomach or neutralise the gastric secretion. Both the acetate and the citrate are used in large doses (30 to 50 grm. per day) to raise the alkalinity of the blood in conditions of acidosis, *e.g.* in **diabetic coma** without upsetting the stomach or causing diarrhoea which very often happens when bicarbonate of soda is used in large doses.

Citrated blood is used for transfusion. The blood of the donor being kept uncoagulated by the use of Injectio Sodii Citratis Anticoagulans.

Kidneys.—All these salts are used to make the urine alkaline. Thus they are used to prevent precipitation of uric acid in cases of **uric acid diathesis** and also to dissolve small uric acid calculi in the kidneys or bladder.

They are largely used in febrile conditions for their diaphoretic and diuretic properties* and also in general

*Sod. Cit. gr. 20
Pot. Acet. gr. 20
Liq. Ammon. Acet. Dil. ms. 120
Syr. Aurant. ms. 30
Aqua Chlorof. ad oz. 1

anasarca. Acetate however is less palatable than the citrate. By reducing the acidity of the urine they relieve irritability of the bladder, and are used in cystitis, and gonorrhoea in the early stage, and to prevent frequent micturition. For the same reason they are used in *Bact. coli* infection of the urinary tract, but large doses are required to maintain the alkalinity of the urine. Since potassium ion may be retained in the blood in case of patients with damaged kidneys, it is desirable to use sodium salt in preference to potassium to avoid toxic effects from the potassium ion.

POTASSII CHLORAS. (Pot. Chloras).—Potassium Chlorate. $KClO_3$.

Characters.—A white powder, or colourless crystals ; taste, cool and saline. With organic or readily oxidisable substances liable to explode if heated or subjected to concussion or trituration. *Solubility.*—1 in 16 parts of water ; almost insoluble in alcohol (90 p.c.), soluble in 30 parts of glycerin.

Incompatibles.—Explodes when rubbed with sulphur, sulphides, charcoal, sugar, tannic acid, ammonium chloride, glycerin, mineral acids and ferrous salts.

B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

OFFICIAL PREPARATION

1. **Tabellae Potassii Chloratis.—B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.** When the quantity in each tablet is not mentioned, 5 gr. tablet shall be supplied.

NON-OFFICIAL PREPARATION

1. **Gargarisma Chlori, B. P. C.** *Syn.—Chlorine Gargle.*—Pot. Chloras 22.9 grm., Acid. Hydrochlor. 4.2 mils, Distilled Water to 1000 mils. Generate chlorine gas by mixing chlorate and acid, and dissolve gradually in water.

PHARMACOLOGY

Externally.—Coming in contact with a septic surface or discharge, the chlorate is decomposed, and oxygen is liberated. This nascent oxygen then acts as a stimulant and antiseptic to septic tissues, but it is not an antiseptic in the ordinary sense of the term, as outside the body it has very little effect even upon the most sensitive bacteria.

Internally. **Gastro-intestinal tract.**—In small doses, potassium chlorate has no action, but in concentrated solution it may through its local salt action cause severe nausea and vomiting, and after absorption considerable diuresis may arise from a similar action on the kidneys.

Blood.—After a moderately large dose it disintegrates the red blood-corpuscles and converts haemoglobin into methaemoglobin, which is set free in the serum. This effect is also observed when chlorate is added to a little drawn blood and shaken up, the mixture soon becoming reddish-brown (chocolate colour) and shows the spectrum of methaemoglobin and later of haematin. When this change takes place in the vessels the oxygenating power of the blood is reduced and asphyxia threatens. When however sufficient haemoglobin remains to continue the respiration of the tissues the subacute form of poisoning results from haemolysis ; as a result of which the renal tubules become blocked with masses of haemoglobin and fragments of the

corpuscles, causing either casts to appear in the urine, or total suppression.

Kidneys.—In moderate doses (15 to 20 grs.) it acts as a diuretic, and more powerfully during pregnancy. In toxic doses, the kidneys become congested, the urine becomes bloody or dark-coloured, and at last there is complete suppression due to blockage of the tubules with degenerated corpuscles. Death occurs usually from uraemia.

Elimination.—Very little is utilised in the blood and tissues, so that about 90 p.c. of the amount given is recovered from the urine. It is also excreted in the saliva, sweat, milk, tears, and nasal mucus.

Toxic action.—It may give rise to dangerous symptoms in individuals after a single large dose, or from repeated small doses; 15 grs. caused death in a child, while an ounce has been taken without any bad effect. The toxic symptoms are nausea, vomiting, diarrhoea, scanty urine or complete anuria; urine becoming a deep reddish-brown colour due to the presence of haemoglobin, methaemoglobin and haematin in solution. Icterus may appear, and the patient may die from uraemic symptoms even as late as a week after the appearance of first symptoms. All these symptoms are dependent on the action of the chlorate on the haemoglobin. Death may result from two causes:

1. From respiratory failure and *asphyxia*, by a rapid breaking down of the red blood-cells and resulting inability of the blood to carry a sufficiency of oxygen.
2. From *uraemia*, owing to complete or partial suppression of urine following an obstruction of the renal tubules, by haemoglobin and fragments of corpuscles.

Fatal Dose.—10 grm. toxic; 15 to 30 grm. fatal to adult.

Therapeutics

Locally.—The chief local use of potassium chlorate is in the treatment of different mouth and throat troubles, such as aphthous stomatitis, follicular tonsillitis, and in the tenderness and inflammation of the gums which follow the prolonged use of mercury. A lotion (10-15 grs. to 1 oz. of water or any astringent infusion) is used as a gargle for such cases. The tablets may be slowly sucked in hoarseness of the throat.

These catarrhal conditions of the mucous membrane of the mouth and fauces are greatly benefited if the local treatment is combined with internal administration, for the salt is excreted with the saliva after absorption, and thus locally influences the disease. How it acts is not clearly understood, and the theory of its acting as an oxidising agent can hardly be explained on any rational ground. It is possible that its effects are due to salt action.

Sometimes it is useful in cases of **habitual abortion.**

Prescribing hints.—Potassium chlorate, being a strong oxidising agent, when prescribed with syrup of ferrous iodide, liberates iodine and forms a precipitate of hydroxide of iron. With iodide of potas-

sium it forms a poisonous compound in the body probably, iodate of potassium.

POTASSII NITRAS. (Pot. Nitras).—Potassium Nitrate. KNO_3. **Syn.**—Purified Nitre; Saltpetre; *Shora*, Beng.

Characters.—White, crystalline powder, or colourless crystals. Taste, cool, saline. Solubility.—1 in 4 of water.
B. P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Non-official Preparation

1. **Pulvis Lobeliae Co., B. P. C.** *Syn.—Asthma Powder.*—Potassium Nitrate 25, Lobelia and Stramonium leaves in coarse powder each 25, Tea leaves in coarse powder 25, Oil of Anise 0.1, Boiling Distilled Water 25. Dry. One tea-spoonful may be burnt to fumigate a bedroom, or the fumes inhaled in *asthma*. This is a supposed imitation of **Himrod's, Bliss's** and the **Green Mountain Cure.**

Pharmacology

Internally. **Gastro-intestinal tract.**—It has a cool saline taste, and in ordinary doses taken in concentrated solution may give rise to gastro-enteritis with the presence of blood in the vomit and stool, muscular weakness, collapse, even coma and death. The same large doses, if taken freely diluted, cause none of these symptoms.

Skin and kidneys.—It is slightly **diaphoretic**, but has a powerful **diuretic** action. Diuresis is due partly to salt action which increases the exchange of fluids between the blood and lymph, thus promoting the filtration in the kidney. Practically the entire quantity is excreted unchanged, a small portion may be reduced to nitrites. Some pass out with the saliva and sweat.

Therapeutics

Internally.—As a diuretic it is chiefly used in conjunction with other diuretics, but the acetate and citrate are always preferred. It is a useful remedy for arresting the onset of a gouty attack, or for removing the headache due to a debauch. 20 grs. of nitrate with 30 grs. of potassium bicarbonate in a tumbler of soda water is the best method of administration in such cases. Nitrate is largely used in the form of Pulv. Lobel. Co. to cut short an asthmatic fit. For this purpose they are burnt and the fumes inhaled.

Caution.—Its use is to be avoided in inflammation of the stomach, intestines, bladder and kidneys, and cardiac weakness.

SODII CHLORIDUM. (Sod. Chlorid.). NaCl. Syn.—Common Salt.

Characters.—Sodium Chloride **is found in small, white, crystalline powder, or** transparent, cubical crystals, **free from moisture. Taste, saline. Odourless.** *Solubility.*—**1 in 3 of cold water, 1 in 10 of glycerin.**
Enters into.—Inj. Sod. Cit. Anticoag. and Inj. Sod. Lact. Co.

Official Preparations

1. **Injectio Sodii Chloridi.** *Syn.—Normal Saline Solution; Physiological Saline Solution.*—Sodium chloride 0.9 p.c. Should be used within one month after its preparation, and if kept in sealed containers for a longer period.
2. **Injectio Sodii Chloridi Composita.** *Syn.—Ringer's Solution for Injection.*—Should be used within a month of its preparation, and if kept in sealed containers, for a longer period.

Non-official Preparations

1. **Liquor Dextrosi et Sodii Chloridi.**—*Syn.*—*Glucose-Saline Solution.*—Dextrose 50 ; sodium chloride 9 ; sterile water to 1000.

2. **Liquor Ringer-Locke.** *Syn.*—*Ringer-Locke Solution.*—Sodium chloride, 9.0 ; potassium chloride, 0.42 ; calcium chloride, 0.24 ; Dextrose, 1.0 ; sodium bicarbonate, 0.5 ; distilled water to 1000. Isotonic with the serum of mammalian blood.

Salt Action

We have already seen that soluble inorganic salts in solution produce their action by being dissociated into ions, and that the effect is a specific chemical action depending upon the potency of the dissociated ions. The *salt action*, on the other hand, produces its effects by changing the osmotic conditions of the solution and is a purely physical phenomenon, no chemical reaction taking place. This action occurs not only with substances which are dissociable (e.g. sodium chloride), but also with non-dissociable compounds (e.g. sugar, urea, etc.).

In the body the epithelial cells of mucous membranes, the endothelial cells of vessels, and the cells of the renal glomeruli act as semipermeable membrane, *i.e.* a membrane through which the solvent can pass, but none or very little of the dissolved substance. If two equimolecular solutions are separated by such a semipermeable membrane, the osmotic pressure is equal on the two sides, and the solutions are then said to be isotonic, and no exchange of constituents occurs between the two fluids. Pharmacologically the term *isotonic* means a solution having the same osmotic tension as that of the blood. If however a given volume of one of these fluids has a higher molecular concentration than the other, it is said to be *hypertonic* (or hyper-isotonic) and an interchange between the two fluids takes place, water being attracted from the hypotonic to the hypertonic solution, and to a smaller extent the substances held in solution pass from the hypertonic to the hypotonic solution, thus shortly rendering the two fluids once more isotonic.

In the human body the process of osmosis is continually going on whenever fluids of varying tonicity meet. As an example, red blood cells shrink in size when they are placed in a solution of salt stronger than blood plasma (hypertonic) because the water is withdrawn from them. In hypotonic solution they swell up as they absorb water and eventually burst liberating haemoglobin to the surrounding tissues, while in isotonic solution they remain unaltered in size.

The muscles are similarly affected, hypertonic solutions withdraw fluid, while weaker ones are absorbed into the muscle. As the muscles are rendered dry and hard and thus unsuitable for microbic growth, salting is used in the preservation of meat and fish. Strong salt solu-

tions by withdrawing their fluid contents irritate the exposed nerves.

As these osmotic exchanges are continually going on in the human body, its importance in the preservation of the balance of the constitution of the body fluids can hardly be exaggerated, and as has been pointed out it is purely a physical process which goes on passively without the expenditure of vital activity which entails a drain of energy of the organism. Thus the process of osmosis may be regarded as a great conservator of energy, of respiratory interchange, and metabolism.

PHARMACOLOGY OF SODIUM CHLORIDE

The body contains 250 grm. of sodium chloride which is an essential constituent of the body and perhaps the chief mineral constituent of the blood serum. It helps to maintain the water and salt balance of the tissues, which is regulated by the posterior pituitary. Sodium metabolism is intimately related to the adrenal cortex, and its hormone, *corticosterone*, maintains the concentration of sodium, potassium and chlorine in the blood. Its deficiency causes retention of potassium and diminution of sodium. The balance in the blood is kept uniform, and some stored in the tissue as reserves, but the surplus water and salt passes out through the kidneys producing diuresis. It is therefore essential that the necessary supply of this substance should be introduced either with the food itself, or as an addition to the food. As it is always present in the body in large quantities and exerts no specific action, it presents a perfect example of salt action which action varies in proportion to the concentration of salt in solution.

Alimentary tract.—Salt has a characteristic taste and strong solutions are astringents. It has very little effect on digestion, and the absorption of food is very little altered when salt is added to food. It is possible, however, that a small quantity of salt in the food may render it more palatable and thus induce a reflex flow of gastric juice. Strong concentrated solutions withdraw fluid from the mucous membrane of the stomach causing shrinkage of the cells and thus produce irritation and act as emetics. Very little is absorbed from the stomach. There is a constant tendency of fluid and some salts to pass inwards from the lumen of the bowels, and being of lower osmotic pressure than the blood serum, hypotonic solution is absorbed from the bowel readily; isotonic solution is more slowly absorbed; while hypertonic solution is absorbed with difficulty, not till it has withdrawn fluid and increased in volume to make it isotonic. This accumulation of fluid may cause purgation, but since it is easily absorbed purgation rarely follows.

Blood.—The changes on the blood after an intravenous injection depend upon the nature of the solution used, whether *isotonic*, *hypertonic*, or *hypotonic*. When a hypertonic solution is used, the blood becomes concentrated, and draws more lymph into the blood by osmotic attraction to regain its normal composition ; this increased volume of the blood in its turn tends to augment the flow of lymph, urine and sweat ; and since the normal balance of plasma and corpuscles must be restored, it sets up currents between the blood and the fluid of the surrounding lymph. All these changes are accompanied by a large rise of capillary pressure in the abdominal viscera and it is possible that the inward flow of lymph is the outcome of this pressure.

As a result of these changes in the blood and lymph there is an increased activity of the excretory organs. Thus there is a copious **diuresis** following an injection of salt solution. It has been suggested that diuresis is the result of increased volume of blood and lymph causing an inward capillary pressure in the glomeruli. But the more plausible explanation is that the presence of salt and water in excess in blood, following an injection, leads to an increased interchange of water between the tissues and blood making the latter diluted, thus decreasing the colloidal constituents of the blood and allowing better filtration.

Cerebrospinal pressure.—Injection of hypotonic solution or distilled water in a vein causes transient increase of venous pressure and a marked and prolonged rise of cerebrospinal fluid pressure. If hypertonic (30 p.c. NaCl) solution is injected intravenously the cerebrospinal fluid pressure after a short rise falls profoundly and remains low for a period of several hours. This effect is independent of the arterial pressure and is probably due to (*a*) rise of the osmotic pressure of the blood causing fluid from the brain substance and cerebral spaces to pass into the blood vessels, or (*b*) reverses the normal direction of the cerebrospinal fluid flow.

Elimination.—Salt is excreted chiefly by the urine, a small portion being lost by the faeces and sweat. Its excretion is diminished in some cases of nephritis, in pneumonia and during growth of new tissues (cancer). Its excretion is hastened by the administration of bromides, iodides, nitrates and thiocyanates, while its use hastens the excretion of these salts, and may thus be useful in bromism and iodism. The chloride concentration in the blood is maintained through the adjustment of the excretion and reabsorption by the tubules.

THERAPEUTICS

Salt being mild irritant, sea bathing acts as a general stimulant to the skin by improving the circulation and nutrition and produces a reflex tonic effect. This is the common experience after sea bath. If the patient is unable to proceed to the sea side, Tidman's sea salt, or ordinary rock salt (one pound to three gallons of water), is an efficient substitute. It is doubtful if salt baths exert any influence on metabolism although it is often recommended in diverse conditions. At Droitwich and Nantwich concentrated hot salt baths (20 p.c.) are used for **chronic rheumatism, sciatica,** and **joint diseases** where the patients not only have daily baths but drink sufficient water on the idea that the tissues will be more thoroughly washed out and waste products will be removed from the system. It is doubtful if this helps more excretion of uric acid from the system, but the fact remains that patients do show improvement under such treatment. The reasons for improvement are perhaps change of climate, a well regulated life and the faith in the healing power of salt water.

Wright's solution (sodium chloride 4, sodium citrate 1, water 120), or hypertonic saline is used in the physiological treatment of septic wounds, and as lotions for washing ulcers and sinuses, specially in diabetics where strong antiseptics damage the tissue. Efficiency of this treatment is due to the hypertonic saline acting as a lymphagogue, which liberating a tryptic ferment from the leucocytes cleanses the wound and checks microbal growth.

Eighty grains (0.9 p.c.) of common salt in one pint of water constitutes normal saline solution, which is isotonic with the blood, and may be injected either into the veins, the rectum, or the loose connective tissue under the axilla or breast, in (1) **shock or collapse** from any cause, such as severe haemorrhage or dehydration, to restore the fluid needed for the heart to work efficiently; (2) certain **toxaemic conditions**, *e.g.* uraemia or eclampsia; (3) **carbon monoxide poisoning**; (4) profound **malnutrition** and **prostration.**

Hypertonic saline solution has been used intravenously in **cerebral oedema** and increased **intracranial pressure.** For the relief of urgent symptoms in cerebral tumour, uraemia and meningitis, it has been given intravenously (30 mils of 20 to 30 p.c. solution). It has been used in cases of head injury, post concussional syndromes, and in severe headaches of various types. Although it relieves headaches associated with these conditions within 5 to 10 minutes, the effects however pass off after one-half to two days when further injections

* Weed and Mckibben, *Amer. Jour. Physiol.*, 1919, 512.

are required to maintain the improvement. On the other hand *hypotonic saline* injections will relieve headache due to withdrawal of spinal fluid by raising cerebrospinal pressure. It has however been shown that the fall of pressure is followed by a rise with secondary oedema of the brain due to the fixing of the salt by the brain cells.*

In the treatment of shock its value is not very favourable and the blood pressure is not maintained for long; moreover large injections may cause fatal dilatation of the heart. In temporary collapse, its value is better.

In conditions of toxaemia it does not help elimination of poison by itself, though it may cause considerable dilution of the poison. It is commonly given intravenously, the usual quantity introduced being 500 to 1500 mils (1 to 3 pts.). The addition of 0.5 p.c. of sodium bicarbonate to the physiological saline solution approaches more closely the normal reaction of the blood and counteracts acidosis.

The effects of these saline infusions vary according to whether the volume of the blood has been previously decreased or not. If there has been no previous diminution in the volume of the blood, a saline infusion has no effect in raising arterial pressure and may lead to anasarca. On the other hand if the volume of blood has been diminished by haemorrhage, a saline infusion will increase the volume of the blood and so maintain arterial pressure.

Since colloids leave the vessels slowly and help to retain the transfused fluid, they diminish diuresis, lymph filtration and oedemas. Acacia and gelatin therefore were added to saline solution to maintain the blood pressure for a longer time in cases of **shock** and **haemorrhage** than when treated with plain non-colloidal saline infusion. Severe and even fatal reaction after the use of acacia, some from faulty technique and others from special susceptibility to the drug, have been recorded. It alters the colloidal equilibrium of the blood which tends to agglutination of the corpuscles and to other anaphylactoid phenomena (Hanzlik).

Sodium chloride is very largely used and with very good results, in the treatment of **cholera**, in which as much as 1500 mils (three pints) of hypertonic solution are used. The usual formula for hypertonic solution consists of sodium chloride 120 grs., potassium chloride 6 grs., calcium chloride 4 grs. to 1 pt. of water. To this is added sodium bicarbonate 40 grs. and glucose 14 grs. The bicarbonate of soda maintains the alkaline buffer-value of the blood and counteracts tendency to acidosis. In cases of severe shock or collapse a small infusion containing adrenaline helps to promote the maintenance of blood pressure. It is also used intravenously, subcutaneously, or per rectum in other

* H. Hoff, *Medical Annual*, 1934.

forms of dehydration, as for instance in acute bacillary dysentery. Besides overcoming collapse, the chloride combines with the toxins and helps them to be excreted *via* the kidneys. Salines should not be given in any form of oedema, especially that of the lungs.

Caution.—Although salt solution is of value in dehydration, its use has certain limitation since dehydration may be due either to salt deficiency or water deficiency. This is specially important in the treatment of dehydration of children following an acute attack of diarrhoea. In this condition water rather than salt depletion is the predominating feature and administration of isotonic saline makes the cells more anhydraemic because more water is sucked out of the already depleted cells and the kidneys are unable to transport sufficient salt into the urine to handle the excess. If however diuresis follows more fluid will be lost and the intracellular dehydration may become worse. Glucose solution on the other hand, when administered to a patient with salt depletion increases excretion of fluid by the kidneys carrying with it enough additional salt to provoke salt depletion shock.

Internally.—Common salt and water is an excellent **gargle** for chronic relaxed throat, and also a very effective nasal douche. It is a prompt and efficient **emetic**, and it may be injected into the rectum for the cure of threadworms. It is an antidote in *poisoning by silver nitrate* which it converts into the insoluble chloride. Since chlorides replace bromides, sodium chloride is used in bromide intoxication.

Since there is loss of sodium chloride from the body and a corresponding increase of potassium in patients suffering from Addison's disease, sodium chloride is used in the treatment of Addison's disease in doses of 75 to 300 grs. (5 to 20 grms.) by the mouth daily with injections of deoxycortone acetate in smaller doses. Only disadvantage is the local irritant effects on the stomach. A suitable method of supplying sodium is to give the chloride 10 grms. (150 grs.) with sodium citrate 5 grms. (75 grs.) in 1 litre (35 oz.) of water and flavoured with some fruit juice.

Saline solution is introduced into the rectum, not more than 4 oz. at a time, either alone or with dextrose (1 oz. to 1 pt.) to maintain the strength of the patient, to combat dehydration, and to act as a diuretic.

Note.—Since retention of salt in the tissues may lead to oedema, a salt free diet has been recommended to reduce oedema with salt retention. Salt free diet sometimes lowers blood pressure and has been advised in primary hypertension.

Untoward effects.—Excessive injection of salines may produce glycosuria, slight fever and rarely albuminuria. It may cause death by pulmonary oedema, and over-distension of the heart.

SODII THIOSULPHAS. (Sod. Thiosulph.). $Na_2S_2O_3, 5H_2O$. (Not official).

Characters.—Colourless, transparent, monoclinic, prismatic crystals ; odourless ; taste, saline. Efflorescent in warm dry air ; slightly deliquescent in moist air. Soluble in 0.5 part of water at 25°C. ; insoluble in alcohol (95 p.c.).

Dose.—5 to 15 grs. or 0.3 to 1 grm. by *subcutaneous, intramuscular or intravenous injection.*

Action and Uses

Sodium thiosulphate has been used in the form of a lotion (1 in 10) as a **parasiticide** in various skin affections, *e.g.* chloasma, ringworm, eczema, furunculosis, etc. It is used in **exfoliative dermatitis**, specially those appearing after the use of organic arsenic preparations, and also against other manifestations of arsenic poisoning, intravenously in doses of 0.3, 0.45 and 0.6 grm. in 5 mils of distilled water every second or third day. It may be administered in 15 gr. doses by the mouth dissolved in normal saline. It has been used in mercurial and bismuth stomatitis and is useful in all acute poisoning from metals. It acts by dissolving the storage depots and helping elimination by the kidneys; but when a large dose is used a large quantity is suddenly dissolved out which the kidneys cannot eliminate so that it actually increases the poisoning. It has been used intravenously in **cyanide poisoning**, when it forms sulphocyanate which is practically nontoxic. **Calcium Thiosulphate**, 5 mils of 10 p.c. solution is also used intravenously in place of sodium thiosulphate.

SODII SULPHOCYANAS. (*Not official*). **Syn.**—Sodium Thiocyanate. Sodium Rhodanate.

Dose.—1 to 5 grs. or 0.06 to 0.3 grm.

Uses.—Supposed to be one of the most efficacious remedies in the treatment of **hypertension** in doses of 5 grs. three times daily after meals, but it has not proved a success. Sometimes nausea, gastro-intestinal disturbances and nervous irritability may follow its use. Others suffer from diarrhoea, muscular fatigue, motor aphasia, hallucination of sight and hearing, delirium, convulsive twitchings, coma and death. In some cases the symptoms resemble those of iodism. The **potassium salt** causes more distressing nausea and weakness. If the patient does not show any satisfactory improvement after 5 gr. doses, taken for two months, the drug will have no effect.

AMMONIUM

Ammonia. (*Not official*)

Ammonia preparations may be grouped into two classes, (*a*) those that liberate irritating ammonia from their compounds, and whose action therefore depends upon free ammonia ; (*b*) those forming salts homologous with alkali metals, and which act as salts in the body.

1. Preparations whose actions depend upon free ammonia

LIQUOR AMMONIAE FORTIS. (Liq. Ammon. Fort.).—Strong Solution of Ammonia is a gas dissolved in distilled water. Contains 32.5 p.c. of w/w ammonia.

Characters.—A clear, colourless, alkaline liquid ; odour, characteristic ; very pungent.

Incompatibles.—Acids and acid salts, metallic salts and alkaloids.

Official Preparations

1. **Liquor Ammoniae Dilutus.** *Syn.—Liquor Ammoniae ; Ammonia Solution.*—10 p.c. w/w of ammonia.
2. **Linimentum Camphorae Ammoniatum.**—25 p.c. Liq. ammon. fort.
3. **Spiritus Ammoniae Aromaticus.**—*See* Ammonium Bicarbonate, page 93.

nazom.-

PHARMACOLOGY

Locally.—A solution of ammonia when rubbed in or applied to the skin stimulates the peripheral nerves and superficial blood vessels, producing a sensation of heat and redness. Being more volatile than the fixed alkalies it penetrates more rapidly and deeply and is corrosive in its effects. If it is concentrated and evaporation prevented it does not dissolve the epidermis but penetrates through it and produces blister. Ammonia is therefore a **rubefacient and vesicant.**

Nose and air-passages.—The vapour of ammonia powerfully **irritates** the mucous membrane of the nose and air-passages causing sneezing. It also irritates the conjunctiva producing lachrymation. By exciting the nasal afferent nerves, it **reflexly stimulates circulation** and **respiration**, and accelerates the pulse rate. If the inhalation is prolonged, or the vapour is too concentrated, inflammation of the nasal and air-passages results.

Internally.—On reaching the stomach, ammonia at once reflexly stimulates the heart and circulation through the accelerator centre. Like other alkalies it neutralises the acidity of the gastric juice if given during digestion, with the formation of ammonium chloride. It also increases peristalsis, helps expulsion of gas, and causes a sense of warmth in the stomach. Therefore, it is an **antacid, gastric stimulant and carminative.** In large doses **it is a gastro-intestinal irritant.**

Absorption.—Although ammonia is readily absorbed from the alimentary canal it does not produce any special physiological effect when administered through this channel. If not converted into a chloride by the acid in the stomach it appears in the portal blood as carbonate or carbamate, and carried to the liver where it is converted into urea. The liver is therefore an important factor in the disposal of ammonia, and if the organ is functionating properly, it can prevent the passage of ammonia to the systemic circulation. The systemic effects are only observed after subcutaneous or intravenous administration. ((*See* Ammonium Chloride).

Blood.—Since ammonia is converted into urea its action differs from the fixed alkalies in not increasing the **available alkalinity of the blood.**

Heart and circulation.—The immediate result of the reflex effect on the vagus, vaso-constrictor and accelerator centres is a rise of blood pressure, but the rate of the heart is variable depending whether the vagus or accelerator stimulation predominates. But owing to the rapid change of the drug in the system this action is of momentary duration.

Lungs.—After inhalation, or when swallowed, ammonia reflexly stimulates the respiratory centre from local

irritation. Respiration is also increased by direct stimulation of the respiratory centre after absorption.

Nervous system.—Ammonia is a **general stimulant**, and by its action on the medulla, it stimulates respiration, constricts the peripheral arterioles, and raises the blood-pressure ; these effects are reflex. In toxic doses, it produces convulsions, due to the stimulation of the motor cells in the cord.

Kidneys.—Since ammonia and its salts are changed into urea they do not increase the alkalinity of the blood and having no effect on the urine except to increase the urea and thus causing some **diuresis.**

Elimination.—Ammonia is thrown off with the breath, sweat, urine and bronchial secretion.

Toxic action.—If a large dose of a concentrated solution be swallowed, it may cause death within a few minutes from suffocation due to spasm of the glottis. Otherwise the symptoms are those of poisoning by a corrosive alkali.

Antidotes.—The same as those of the other alkalies.

THERAPEUTICS

Externally.—As a *local stimulant* to nerve and blood vessels, the liniment of ammonia is rubbed over stiff joints, and in various conditions of chronic rheumatism ; and as a *counter-irritant* on the chest in bronchitis, pneumonia and pleurisy. Ammonia may be used as a *vesicant* in cases where cantharidin is contra-indicated. A piece of lint cut slightly larger than the intended blister is moistened with the strong solution and applied and immediately covered over with a watch-glass. Ammonia neutralises the poison of nettles and insect bites and thereby lessens the pain and swelling caused by them.

In the form of inhalation (smelling salts) it is used to rouse patients from fainting, shock, syncope, stupor and narcotic poisoning.

Internally.—Like other alkalies, ammonia may be given in acid dyspepsia. Spirit of sal volatile is a useful remedy for gastric and intestinal cramps : a few drops with bicarbonate of soda and dill water give relief to flatulence in infants. As a general diffusible stimulant, ammonia is extremely serviceable in syncope, shock, fainting, and in the low adynamic conditions of febrile diseases, *e.g.* pneumonia, typhoid, etc. It makes an excellent "pick-me-up,"* and softens the phlegm in bronchitis and catarrhal pneumonia, but the bicarbonate is better. Ammonia controls *iodism*, and is therefore combined with iodides when prescribed in large doses.

*Sp. Ammon. Aromat	ms. 30
Sp. Ether.	ms. 15
Sp. Chlorof.	ms. 15
Tinct. Cardam. Co.	ms. 30
Aqua Camph.	ad. oz. 1

AMMONII BICARBONAS. (Ammon. Bicarb.).—Ammonium Bicarbonate may be prepared by passing carbon dioxide into solution of ammonia. Contains not less than 98 p.c. of ammonium bicarbonate.

Characters.—White crystals, or fine, white crystalline powder. Taste, pungent, odour ammoniacal. Slightly hygroscopic. Volatilises slowly at ordinary temperature. *Soluble* in 5.5 parts of water ; insoluble in alcohol (90 p.c.).
B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

Official Preparations

1. **Liquor Ammonii Acetatis Fortis.**—*See* page 95.
2. **Spiritus Ammoniae Aromaticus.** *Syn.—Spirit of Sal Volatile.*—Contains 1.25 p.c. w/v of ammonia. **B. P. Dose.**—15 to 60 ms. or 1 to 4 mils.

Pharmacology and Therapeutics

Internally.—The bicarbonate possesses all the virtues of the liquor, and in addition is a powerful **expectorant,** facilitating the expulsion of viscid mucus. The expectorant action is reflex from irritation of the stomach. The bicarbonate and the aromatic spirit of ammonia are therefore very useful in bronchitis and catarrhal pneumonia.* In the form of aromatic spirit of ammonia it is used as a mild stomachic in debility and alcoholism, and as a carminative.

Prescribing hints.—The bicarbonate of ammonia and the spiritus ammoniae aromaticus are incompatible with acids and should not be prescribed with any syrup with an acid reaction, *e.g.* syrup of squill. Although carbonates precipitate free alkaloid from watery solution of most alkaloidal salts, codeine and atropine are not precipitated. Syrup of tolu or liquid extract of liquorice cover its taste well. When ammonium carbonate is prescribed, ammonium bicarbonate shall be dispensed.

2. Preparations which act as salts in the body

AMMONII CHLORIDUM. (Ammon. Chlorid.). Ammonium Chloride. NH_4Cl. Syn.—Sal Ammoniac ; *Nishadal*, Beng.

Characters.—White, crystalline, granular powder ; odourless ; taste, saline, cooling. *Solubility.*—1 in 3 of water, 1 in 60 of alcohol (90 p.c.).
Incompatibles.—Alkalies and their carbonates, mineral acids ; lead and silver salts.
B. P. Dose.—5 to 60 grs. or 0.3 to 4 grms.

Non-official Preparation

1. **Lotio Ammonii Chloridi.** *Syn.—Lotio Evaporans, B.P.C.*—Ammonium chloride gr. 300 ; alcohol (90 p.c.) oz. 2.5 ; water to oz. 20.

Pharmacology and Therapeutics

Since ammonium is converted into urea the systemic action of ammonia base is elicited when the chloride is injected intravenously or subcutaneously. It first stimulates and then paralyses the central nervous system and the **medulla** ; increases the reflex excitability of the cord, and causes convulsions like strychnine. The motor nerve-endings are paralysed in frogs, though no such effect is observed in mammals. During convulsion the respiration is arrested and the blood pressure rises enormously. Death takes place from asphyxia, but if the animal is kept

*Liq. ammon. acet. dil.	ms.	120
Ammon. bicarb.	gr.	4
Pot. bicarb.	gr.	15
Tinct. ipecac.	ms.	10
Syr. tolu	ms.	30
Inf. seneg.	ad. oz.	1

alive by artificial respiration recovery takes place owing to elimination of the salt.

The rise of blood pressure is due to constriction of the peripheral vessels through the vaso-motor centre, and the heart becomes slow from stimulation of the vagal centre from increased blood pressure.

Externally.—Locally applied, a solution of the chloride has a soothing refrigerant effect, and this effect is greatly increased by the addition of alcohol or potassium nitrate. A lotion is therefore used in cases of injury to different parts, such as sprains, bruises, etc., as a cooling application, and Lotio Evaporans is used for the purpose.

Internally.—It is an irritant and astringent and causes a reflex flow of saliva. From the stomach it is rapidly absorbed and is converted into urea but not to the same extent as when the bicarbonate is used. It thus liberates chlorine ions to combine with sodium and potassium, forming chlorides and are eliminated as such, thus *reducing the fixed alkalies* of the body giving rise to acidosis. Because it causes acidosis and helps the plasma to hold more calcium in solution it is used in **tetany** and to counteract **alkalosis.**

In the form of lozenges, when allowed to melt slowly in the mouth, it acts as a **reflex expectorant.** In moderate doses (10 to 15 grs.), it is a gastro-intestinal irritant, particularly to the intestine.

Liver.—It is used as an indirect cholagogue in catarrhal jaundice, and at one time was used in the treatment of threatening abscess of the liver. It is doubtful if it possesses any of these effects.

Lungs.—It makes the secretion of the bronchial mucus more fluid and less tenacious and helps expectoration. This effect is reflex from irritation of the stomach. It is therefore used as an expectorant in bronchitis, both acute and chronic. Since its effects do not last long it requires to be repeated frequently.

Kidneys.—It is a **diuretic,** due partly to urea and partly to acidosis which reduces the amount of salts adsorbed by the tissue proteins, and the salts so liberated increase the non-colloidal constituents of the blood which reducing the resistance to filtration act as diuretics. It is used with mercurial diuretics to increase their diuretic effect. The usual method is to administer the salt by the mouth in 15 to 30 gr. doses followed by injection of mersalyl. It makes the urine acid and in 10 gr. doses given several times a day will reduce the pH of the urine to about 5.5. It is therefore used to help the action of mandelic acid or hexamine.

Excretion.—It is partly excreted as such, but a large portion as urea.

LIQUOR AMMONII ACETATIS FORTIS. (Liq. Ammon. Acet. Fort.).—*Strong Solution of Ammonium Acetate.*

Characters.—A clear, syrupy liquid with an odour of ammonia and of acetic acid.

B. P. Dose.—15 to 60 ms. or 1 to 4 mils.

Official Preparation

1. **Liquor Ammonii Acetatis Dilutus.** *Syn.—Liquor Ammonii Acetatis; Mindererus Solution.*—12.5 p.c. of strong solution of ammonium acetate. B. P. Dose.—1/4 to 1 oz. or 8 to 30 mils.

Non-official Preparation

1. **Liquor Ammonii Citratis.**—*Ammonium carbonate* 87.5 G., citric acid 125 G., water to 1000 mils. *Dose.*—2 to 6 drs. or 8 to 24 mils.

Pharmacology and Therapeutics

The solution of the acetate and citrate are diaphoretics and diuretics.* The diaphoresis is due to their effects on the sweat centre. If the patient is kept cool, their action concentrates upon the kidneys and there is diuresis. The diuresis is due to the formation of urea in which form they are eliminated. For these actions, they are used as mild, non-depressant antipyretics in fevers.

LITHII CARBONAS, B. P. C.—In white powder, or minute crystalline grains. Taste, slightly alkaline. *Solubility.*—1 in 80 of water, insoluble in alcohol (90 p.c.).

Dose.—2 to 5 grs. or 0.12 to 0.3 grm.

LITHII CITRAS, B. P. C.—A white crystalline, deliquescent salt. Taste, saline cooling. *Solubility.*—1 in 2 of water.

Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

Action and Uses.—Lithium salts are readily absorbed and resemble the corresponding potassium salts in their actions, and render the urine alkaline acting like other fixed alkalies.

They are diuretics, acting chiefly by salt action, and it was claimed that their prolonged use would dissolve uric acid calculi. But lithium acts as a solvent for uric acid only when present in relatively large amounts, since the quadriurate is not rendered soluble by any lithium salt except in concentrations which would be toxic to man. Moreover, there is no evidence, clinical or otherwise, to show that lithium is more valuable than potassium.

CALCII CARBONAS

(Calc. Carb.)

Syn.—Precipitated Calcium Carbonate. **Syn. I. V.**—*Khari,* Beng.

Source.—Calcium Carbonate is obtained by the interaction of a soluble calcium salt and a soluble carbonate.

Characters.—A white, micro-crystalline powder, insoluble in water. Odourless and tasteless.
Incompatibles.—Acids and acid salts.
B. P. Dose.—15 to 60 grs. or 1 to 4 grms.
Enters into.—Syr. Ferri Phosph. Co. and Troch. Bism. Co.

CRETA. (Cret.). Syn.—Creta Praeparata.—Chalk is native calcium carbonate.

Characters.—White, or greyish-white, friable masses, or powder. No odour or taste.
B. P. Dose.—15 to 60 grs. or 1 to 4 grms.
Enters into.—Hydrarg. c. Creta.

*Liq. ammon. acet. dil.	ms. 120
Pot. acetas vel citras	grs. 20
Sp. aether. nitros.	ms. 15
Syr. aurant.	ms. 60
Aqua chlorof.	ad. oz. 1

Official Preparations

1. **Pulvis Cretae Aromaticus.**—25 p.c. chalk. **B. P. Dose.—10 to 60 grs. or 0.6 to 4 grms.**
2. **Pulvis Cretae Aromaticus cum Opio.**—2.5 p.c. opium or 1/7 gr. morphine in 60 grs. **B. P. Dose.—10 to 60 grs. or 0.6 to 4 grms.**

Non-official Preparations

1. **Mistura Cretae, B. P. C.** *Syn.—Chalk Mixture.*—Aromatic chalk powder 15 gr. chalk 15 gr., tragacanth powder 1/2 gr., cinnamon water q.s. 1/2 oz. *Dose.*—1/2 to 1 oz. or 15 to 30 mils.
2. **Mistura Cretae Aromaticus cum Opio. B. P. C.**—Aromatic chalk powder 20 gr., tragacanth powder 1/2 gr., tinct. opii, tinct. catechu, compound tinct. of cardamom, aromatic solution of ammonia, each, 10 ms., chloroform water, q.s. 1/2 oz. *Dose.*—1/2 to 1 oz. or 15 to 30 mils.

Pharmacology and Therapeutics

Internally. **Alimentary canal.**—Chalk acts as a direct local antacid, neutralising free acids in the mouth and stomach. It passes readily into the intestine, where it acts as an **antacid** and a non-irritating **astringent,** caused by (1) the neutralisation of any acid it meets, with formation of chloride or lactate and thus reducing the secretion ; (2) formation of a protective coating over the intestinal mucous membrane which also diminishes reflex peristalsis ; (3) adsorption of toxins ; and (4) depressant action on the intestinal canal due to calcium ion. Lime salts are feebly absorbed and are excreted with the faeces. As an *antacid* it may be used in acid dyspepsia, but lime water acts much better. Aromatic chalk powder is an excellent remedy for mild diarrhoea, especially that of children with sour-smelling stools. If the diarrhoea is caused by some irritating food, a dose of castor oil should precede its use. In diarrhoea chalk acts like bismuth salts by forming an insoluble coating over the mucous membrane, and may be combined with it.* It is also used as an antacid in hyperacidity and in gastric and duodenal ulcer, often in combination with carbonate or oxide of magnesium (*see* page 77). Lime salts are of special value in acid poisoning, especially in oxalic acid poisoning, as they form insoluble oxalates.

Prescribing hints.—Generally given in the form of chalk mixture with opium and astringent tinctures. Aromatic chalk powder with bismuth and grey powder is very useful in *infantile diarrhoea.*†

CALCII CHLORIDUM. (Calc. Chlorid.). $CaCl_2$.—Calcium Chloride is prepared by neutralising hydrochloric acid with calcium carbonate.

Characters.—In dry, white granules or porous deliquescent masses. Taste, warm, slightly bitter. *Solubility.*—1 in 1.5 of water, 1 in 3 of alcohol (90 p.c.).
Incompatibles.—Carbonates, phosphates, sulphates and tartrates.
B. P. Dose.—10 to 30 grs. or 0.6 to 2 grms.
N. B.—When calcium chloride is prescribed for injection, twice the prescribed amount of hydrated calcium chloride shall be dispensed.

*Bism. carb.	gr. 10	†Hydrarg. c. cret.	gr. 1/8
Pulv. cret. aromat.	gr. 10	Bism. carb.	gr. 2
Pulv. Ipecac. et opii	gr. 5	Pulv. cret. aromat.	gr. 4
For one powder.		For one powder	

N.B.—Dover's powder may be omitted if necessary

Calcii Chloridum Hydratum. (Calc. Chlorid. Hydrat.). $CaCl_2 6H_2O$.

Hydrated Calcium Chloride is obtained by neutralising hydrochloric acid with calcium carbonate, and crystallising the product.

Characters.—Colourless crystals; odourless; taste, slightly bitter. Very deliquescent. Soluble in [illegible] part of water, and in 0.95 part of alcohol (90 p.c.).
B. P. Dose.—*By intravenous injection*:—10 to 30 grs. or 0.6 to 2 grms.
Enters into:—Injectio sodii chloridi co. and injectio sodii lactatis co.

CALCII GLUCONAS. (Calc. Glucon.). $C_{12}H_{22}O_{14}Ca,H_2O$

Calcium Gluconate is the normal calcium salt of gluconic acid.

Characters.—A white, crystalline or granular powder; odourless, tasteless. Soluble in [illegible] parts of water at 25°C., in about 5 parts of boiling water; insoluble in dehydrated alcohol, in solvent ether, and in chloroform.
B. P. Dose.—15 to 60 grs. or 1 to 4 grms.

OFFICIAL PREPARATION

1. **Injectio Calcii Gluconatis.**—Contains 30 grs. in 300 ms. (10.0 p.c.). It is a supersaturated solution and must be free from solid particles. If separation of crystals occurs it should not be used. **B. P. Dose.—150 to 300 ms. or 10 to 20 mils. by intramuscular or intravenous injection.**

CALCII LACTAS. (Calc. Lact.). $C_6H_{10}O_6Ca,5H_2O$.

Calcium Lactate is obtained by neutralising diluted lactic acid with calcium carbonate, and evaporating the resulting solution.

Characters.—A white, almost tasteless powder. ***Soluble*** **in 20 parts of water readily soluble in hot water. Forms a clear colourless solution.**
B. P. Dose.—15 to 60 grs. or 1 to 4 grms.

OFFICIAL PREPARATION

1. **Tabellae Calcii Lactatis.** *Syn.—Tablets of Calcium Lactate.*—**B. P. Dose.—15 to 60 grs.** or **1 to 4 grms.** N.B. if the quantity to be contained in a tablet is not mentioned, 5 grs. tablets should be supplied.

CALCII PHOSPHAS. (Calc. Phosph.). $Ca_3(PO_4)_2$.—Calcium Phosphate is obtained by the interaction of calcium chloride and sodium phosphate in the presence of ammonia.

Characters.—A light, white, amorphous powder. No odour or taste. Insoluble in water.
B. P. Dose.—10 to 30 grs. or 0.6 to 2 grms.

NON-OFFICIAL PREPARATIONS

1. **Syrupus Calcii Lactophosphatis, B. P. C.**—Calcium lactate 75 grms., phosphoric acid 29 mils, sucrose 700 grm., concentrated orange flower water 2 mils, water q.s. to 1000 mils. *Dose.*—30 to 60 ms. or 2 to 4 mils.
2. **Calcium Laevulinate,** *Syn.—Calcium Laevulate.*—Contains 14.83 p. c. Ca. A stable and very soluble salt, easily assimilable. *Dose.*—For *intramuscular injection,* 5 grs. of 15 p. c. solution; for *intravenous injection*, 15 grs. of 10 p. c. solution.
3. **Calcii et Sodii Lactas, B. P. C.**—Occurs as white powder or as colourless, hard granules. Deliquescent. Soluble in 15 parts of water. Action same as other calcium salts but is more soluble and easy of absorption. Specially useful in *night sweats of phthisis, haemoptysis,* and *difficult dentition*, and in certain types of *dermatitis. Dose.*—5 to 30 grs. or 0.3 to 2 grms.

CALCIUM

Calcium is an important constituent of the animal body and it is to the large proportion of calcium phosphate which it contains that the body skeleton owes its most essential property of rigidity. It is present to a considerable amount in all soft tissues and the blood, and is essential to most forms of living matter, and for the activity of certain ferments. Thus the milk will not curdle, nor the blood will coagulate, in the absence of calcium. Important as it is to the body mechanism, provision is made for its supply, and calcium is present in both animal and vegetable foods, although vegetable foods are much richer in calcium than the foods of animal origin. Milk and yolk of eggs are specially rich in calcium in a readily assimilable form. The young animal therefore is freely supplied with calcium at a period of life when it is necessary for its growth. Deficiency of calcium in food, therefore, has a prejudicial

M—7

effect on the growing animals, owing to the larger amount of calcium necessary for the growth of the skeleton during this period although very little untoward effect is observed in grown up animals.

The changes following calcium starvation resemble those observed in rickets in children. In rickets, however, the softness of the bones is not due to any deficiency of calcium in the food, but to lack of sunlight and vitamin D, which prevent the absorption of calcium and phosphorus in balanced proportion, so that lime is not deposited on the bones.

Another condition which resembles rickets of children is sometimes observed in women during the period of pregnancy and lactation. Owing to the excessive demand of the growing child, the mother's skeleton becomes depleted of calcium which becomes soft and spongy, unless this demand is met by proper supply of calcium. This condition is known as osteomalacia, and like rickets is due to deficiency of vitamin D, lack of sunlight and derangement of calcium metabolism.

Pharmacology and Therapeutics

Calcium is present in all tissues, and not only the heart but other tissues of the body are sensitive to disturbances in the amount of calcium and sodium in the blood. Given intravenously in large doses, lime salts lessen the irritability of the cerebral cortex, while deficiency of the calcium in the blood causes increased irritability of the brain with muscular twitchings.

An intravenous injection of chloride in non-toxic doses in man is followed by flushing of the skin and face, a hot feeling over the whole body, constriction of the throat, and sometimes nausea and vomiting. The peripheral vessels dilate and the systolic pressure falls. The heart becomes slow from vagus stimulation which is antagonised by atro-

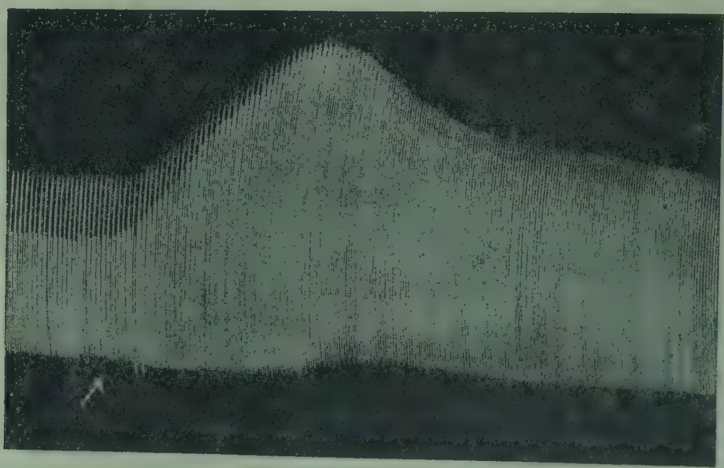


Fig. 2.—Movements of Isolated Rabbit's Heart perfused with Locke's Solution showing effect of Calcium.

At point of arrow a small amount of calcium chloride was administered.

pine, the action resembling digitalis in some respects. Soon, however, the rate becomes normal and even accele-

rated, and the blood pressure rises from stimulation of the sympathetic.

On isolated heart calcium increases its muscular activity and tone, and acts as a tonic. It antagonises the depressant effect of potassium, and its absence stops rhythmic activity of other plain and striated muscles which reappears with increased tone on the addition of calcium. In case of weakness of the cardiac muscle caused either by valvular insufficiency or myocarditis, calcium may be used where digitalis treatment proved unsuccessful. But it should be used at least four days after digitalis treatment.

The **pupils** are contracted from direct stimulation of the sphincter, and probably from partial stimulation of the nerve ending. This is followed by dilatation from sympathetic stimulation. !

All the above effects are elicited by the intravenous injection, and are not so marked when administered by the mouth, due to slow absorption. Calcium antagonises the effect of magnesium and potassium (*see* page 72).

The normal calcium requirement of an adult is about 0.5 to 1 grm. daily. During the growing period, pregnancy and period of lactation the demand is greater. It is absorbed with difficulty and it has been estimated that only 50 p.c. of calcium of the food is absorbed. Therefore 1 grm. of calcium must be taken daily with food to supply the adequate requirement. One litre of fresh cow's milk contains 1 grm. of calcium. Calcium is probably utilised to the extent of 20 to 30 p.c. though it may be much higher in young infants.

Calcium is absorbed with difficulty. Its absorption depends upon the nature of the intestinal contents. During the digestive period the reaction of the upper part of the gut is frequently on the acid side and absorption of calcium takes place in the form of acid calcium phosphate. If the contents of the intestine be alkaline, calcium is precipitated as insoluble carbonate or phosphate, and deficiency of vitamin D retards absorption. Conversely administration of vitamin D increases the absorption of both calcium and phosphorus. If the intestine contains unsaturated fatty acids as derived from cod-liver oil, butter or bacon fat, calcium forms soluble soap and is readily absorbed. Calcium salts of fatty acids though insoluble are absorbed as soluble calcium salts possibly due to their solubility in bile. Calcium metabolism is regulated by ultra-violet rays, and Fusshall* has shown that on a less calcium diet, as compared to controls, irradiated rats showed distinctly better calcium deposition, growth and increased calcium content of the serum.

* *American Journal of Physiology*, 1928.

Calcium is essential to the process of normal coagulation of the blood, which may be prevented by precipitating it by oxalates, citrates and fluorides. It is also necessary for the action of thrombokinase or for the conversion of prothrombin into thrombin. Administered *per os* calcium has no appreciable effect in increasing the calcium content of the blood. Given intravenously or subcutaneously, the blood calcium may remain high for a short time, the strength and duration depending not only upon the amount of calcium given but also on the calcium content of the blood. It has been used in all forms of **internal haemorrhages,** but since lowest blood calcium compatible with life is rarely below that is needed for clotting, administration of calcium has little effect in these conditions. If anything its use is superfluous. In some of these conditions the platelets are more at fault than calcium. Its use has been suggested in haemoptysis, purpura haemorrhagica, haemophilia and aneurism and as a preventive before operation to reduce tendency to bleeding in persons suffering from jaundice. In these cases 10 p.c. of hydrated calcium chloride or gluconate is administered intravenously, about 5 to 10 mils being introduced at a time. The gluconate solution being less irritant may be administered intramuscularly.

Calcium circulates in the blood partly in combination with proteins and partly as diffusible salt. Of the diffusible calcium the portion existing in an ionised form performs the important functions. The normal blood serum contains 9 to 11 mg. of calcium per 100 c.c. and this concentration is constant, and is regulated by the parathyroid hormone, calcium in the food, reaction of the tissues, and vitamin D. In **tetany** following parathyroidectomy the calcium content of the blood is diminished, sometimes falling as low as 5 mg. per 100 c.c., and the symptoms following parathyroidectomy or of tetany may be checked by restoring the blood calcium level to normal by the use of large doses of calcium, or by the injection of parathyroid hormone, or by measures which increase the acid balance of the body, *e.g.* acids, ammonium chloride or calcium chloride, which cause acidosis. It has been shown that the acid-balance determines the concentration to which the plasma can hold calcium in solution. Conversely any change in the reaction of the blood towards alkalosis decreases the amount of *functioning* diffusible calcium without altering the calcium content. In tetany and spasmophilia of children following rickets, good results are obtained by intravenous administration of 5 p.c. solution of chloride or 10 p. c. solution of gluconate. For the same reason it gives relief in other spasmodic conditions, e.g., **intestinal, renal and biliary colics** and also in in-

fantile convulsion which is often due to hypocalcaemia. It may be used in chorea, a disease characterised by low total serum calcium content with corresponding diminution of the calcium content of the cerebrospinal fluid.

The soluble lime salts increase the resistance of the red blood cells to certain haemolytic serums and also lessen the liability to **anaphylactic reaction** in sensitive persons. They are of great value in **bronchial asthma** where they increase the sympathetic excitability in cases with evidence of vagotonia ; and are also useful in hay fever, acute rhinitis, serum disease, and other conditions attended with parasympathetic excitability. It is used in **pleural effusions** on the hypothesis that there is a disturbance of the calcium-sodium balance in the tissues, there being a comparative deficiency of the former and corresponding increase of the latter.

Owing to the constant demand on the part of the growing foetus for calcium, the serum calcium of the mother becomes low, and administration of calcium during pregnancy and the period of lactation protects the mother from calcium deficiency by maintaining the calcium at its proper level.

It is largely used in **pulmonary tuberculosis** on the assumption that the healing of tubercular lesions in the lungs is associated with calcification and that there is excessive excretion of calcium in this disease. There is however no reason to believe that there is any deficiency of serum calcium in this disease, and clinical results are not unanimous. In a certain number of cases a temporary benefit is observed as it reduces the temperature, improves the appetite, checks night sweats, and helps the patient to gain in weight. In intestinal tuberculosis it is used with better results in early cases, but is of no use in severe forms, although it is worthy of a trial. Owing to the deficiency of calcium, its use has been suggested in **sprue** either alone or with parathyroid.

Calcium is useful in **lead poisoning** as it causes elimination of lead from the body by increasing the exchange of calcium and lead between the bones and the blood. It helps storage of lead in an inert form in the bones, and the lactate is given in 30 gr. doses three times a day, or a 5 p.c. solution of chloride or gluconate intravenously. After the acute stage, slowly mobilise the stored lead by low calcium intake and by producing acidosis.

It has some protective action on the liver and its administration prevents damage to the liver caused by carbon tetrachloride.

One of the important specific actions of calcium is its power to retard inflammatory process, and that transudation and oedema are favoured by withdrawal of calcium,

which normally serves to check the permeability of the vessels. Calcium is therefore used in serous headaches, angioneurotic oedema, urticaria, chilblains, and conditions suggesting abnormal permeability of vessels.

The chloride increases the acidity of the urine, as a large part of calcium is converted into carbonate and escapes absorption, the chlorine combines with fixed alkalies to liberate H-ion causing acidosis and may be used in alkalosis. It is a powerful **diuretic** due to increase of non-colloidal constituents of the blood. It has been used in acute and subacute nephritis where the liberated chlorine ions combine with sodium and are excreted as sodium chloride with large amount of water (Cushny).

To promote **nutrition** and cell **growth**, the phosphate is exceedingly useful in the case of children who have overgrown their strength; in women weakened by child bearing, prolonged suckling, or excessive menstruation; and in anaemia and exhaustion brought about by prolonged suppuration, diarrhoea, leucorrhoea, etc.

The phosphate is also used to expedite the union of fractures and the healing of caries of bones.

Excretion of calcium takes place through the intestine mainly (about 75 p.c.) and less with the urine, depending upon whether it forms a soluble or insoluble salt in the intestine. If it forms an insoluble phosphate it is excreted with the stool, whereas if it forms a soluble chloride it is mainly excreted with urine.

Prescribing hints.—Calcium is best given in solution after food. But as all lime salts are feebly absorbed we are doubtful as to the wisdom of giving them in excessive doses as they may derange the stomach. The objection to the use of chloride is the taste. But this is noticed only when concentrated solutions are used. For the treatment of tuberculosis it is given intravenously for prolonged periods in 5 to 10 p.c. solutions; commencing with 2 mils and then working up to 10 mils. Given subcutaneously, or when it leaks into the tissues during intravenous administration, local inflammation and necrosis result, but gluconate does not. For its diuretic effect the chloride is given in large doses (30 to 40 grs.), three or four times a day. Given intravenously the effects are quicker and more definite than oral administration. In urgent cases therefore it should be given intravenously in doses of 0.25 grm. in 5 mils of water. Ordinarily intramuscular injection gives just as good results and the gluconate is used for the purpose. The action of the lactate is somewhat weaker and therefore larger doses are required. Calcium should not be used intravenously simultaneously with digitalis as it may cause fatal results.* Calcium should not be prescribed with carbonates, sulphates, or sp. ammon. aromat. which will throw insoluble precipitates.

CALCII HYDROXIDUM. (Calc. Hydrox.). $Ca(OH)_2$. **Syn.**—Calcii Hydras; Slaked Lime. *Chun*, Beng. *Chunam*, Hind.

Source.—Freshly prepared by the action of water on lime.

Characters.—A soft, white alkaline powder; taste, alkaline and slightly bitter.

* Mengle, *Jour. Amer. Med. Assoc.*, I, 1936.

Solubility.—Slightly soluble in water; *more freely* in solutions of glycerin and of sugars.

Incompatibles.—Vegetable and mineral acids, and metallic salts.

Official Preparation

1. **Liquor Calcii Hydroxidi.** *Syn.—Liquor Calcis; Lime Water.*—0.15 p.c. w/v of calcium hydroxide. A clear, colourless liquid with alkaline taste. Absorbs CO_2 from the air and forms a film of calcium carbonate on the surface. B. P. **Dose.—1 to 4 ozs. or 30 to 120 mils.**

Pharmacology and Therapeutics

Externally.—Unslaked or slaked lime is a **caustic,** but the action is localised. In the form of Vienna Paste (*see* page 74), slaked lime may be used to destroy warts and small epithelial and other growths. Lime water, either with linseed oil (Carron oil), olive oil or glycerin, is a soothing application to burns and scalds. An addition of 1 to 2 p.c. of phenol increases its efficacy. Lime water is a local **sedative** and **astringent** when applied to the broken skin. It makes a soothing astringent dressing for weeping eczema.

Internally. **Alimentary canal.**—The chief action of the oxide and hydroxide is due to the alkalinity and not to the calcium. Like chalk, lime water neutralises free acids of the contents of the stomach and acts as an **antacid,** but more powerfully. It is an **antidote** for poisoning by mineral acids, oxalic acid and zinc chloride.

It is chiefly used as a diluent for milk to make the curd more flocculent (1 in 3 or more), and to check vomiting of infants. In the same way it may be given in enteric diarrhoea and other affections to prevent the milk from forming hard indigestible lumps, but its use has now been replaced by sodium citrate. As an astringent it is useful in mild infantile diarrhoea.

Prescribing hints.—Lime water is ordinarily given in milk. To suckling babies one teaspoonful with an equal quantity of milk may be given every 3 hours before nursing, and to hand-fed ones **a dessert spoonful in each bottle.**

CALX SODICA.—Soda Lime is a mixture of sodium hydroxide, or sodium hydroxide and potassium hydroxide, with calcium hydroxide. It should absorb not less than 20.0 p.c. of its weight of carbon dioxide.

Characters.—In white or greyish-white granules, or it may be coloured with an indicator to show when its absorptive power is exhausted. *Partially soluble* in water; **almost *completely soluble* in dilute acetic acid.**

N.B.—Should be kept in well-closed container.

Uses

When surgical anaesthesia is induced by gases like nitrous oxide, ethylene or cyclopropane, or by ether, the level of narcosis depends upon the tension of these gases in the tissue cells. These are not changed in the body, but are excreted when the administration is discontinued. Since anaesthetic gases are exhaled unchanged from the lungs, the same gas can be used over and over again, but in practice small quantities of gas have to be added to compensate for the losses (*a*) by leakage at joints, *i.e.* defect in the apparatus; (*b*) by diffusion through the rubber rebreathing bag; (*c*) by excretion through the skin and from the surface of the operation wound.

These lower anaesthetic vapour tension in the blood and tissue cells. Total rebreathing, therefore, retains the anaesthetic in the patient, but is not permissible unless the exhaled carbon dioxide is neutralised, and oxygen sufficient to maintain the patient's metabolic need is supplied. Means have to be taken to absorb carbon dioxide and soda lime is used for the purpose. This ensures better control of respiration, while reducing to a minimum the amount of anaesthetic used.

Under average condition 1 grm. of good soda lime absorbs about 88 c.c. CO_2. When the patient's respiration becomes progressively deeper and the pressure rises and soda lime becomes exhausted it should be changed. Some are coloured green and change to brown when they become inactive.

MAGNESII OXIDUM LEVE

(Mag. Oxid. Lev.)

Syn.—Magnesia Levis: Light Magnesia.—Light Magnesium Oxide is prepared by heating light magnesium carbonate to a dull red heat.

Characters.—A very light, white powder ; odourless ; taste, slightly alkaline. Almost insoluble in water.

B. P. Dose.—10 to 60 grs. or 0.6 to 4 grms.

OFFICIAL PREPARATION

1. **Mistura Magnesii Hydroxidi.** *Syn.—Cream of Magnesia.*—Contains 8.25 p.c. w/v of magnesium hydroxide, or 12.5 grs. of magnesium oxide in 240 ms. **B. P. Dose.—60 to 240 ms. or 4 to 16 mils.**

Magnesii Oxidum Ponderosum. (Mag. Oxid. Pond.). **Syn.**—Magnesia Ponderosa; Heavy Magnesia.—Heavy Magnesium Oxide is prepared by heating heavy magnesium carbonate to a dull red heat.

Characters.—A white powder ; almost insoluble in water, but readily dissolved by acids. Insoluble in alcohol (90 p.c.). Odourless ; taste, slightly alkaline.

Incompatibles.—All acids.

B. P. Dose.—10 to 60 grs. or 0.6 to 4 grms.

Magnesii Carbonas Levis. (Mag. Carb. Lev.).—Light Magnesium Carbonate is prepared by boiling together *dilute* aqueous solutions of magnesium sulphate and sodium carbonate.

Characters.—A light, white powder ; odourless ; almost tasteless. ***Solubility.***—Almost *insoluble* in water, insoluble in alcohol (90 p.c.) ; soluble in dilute acids with effervescence.

B. P. Dose.—10 to 60 grs. or 0.6 to 4 grms.

Enters into.—Pulv. rhei co.

Magnesii Carbonas Ponderosus. (Mag. Carb. Pond.).—Heavy Magnesium Carbonate is prepared by mixing boiling *concentrated* solutions of magnesium sulphate and sodium carbonate, evaporating to dryness, and washing the product.

Characters.—A white, granular powder ; odourless and tasteless. Almost *insoluble* in water, and in alcohol (90 p.c.), soluble with effervescence in dilute acids.

B. P. Dose.—10 to 60 grs. or 0.6 to 4 grms.

Enters into.—Pulv. rhei co., Troch. bism. co.

OFFICIAL PREPARATION

1. **Liquor Magnesii Bicarbonatis.** *Syn.—Fluid Magnesia.*—7.5 grs. in 1 oz. A clear, colourless liquid, may effervesce when the bottle is first opened. **B. P. Dose.—1 to 2 ozs. or 30 to 60 mils.**

MAGNESII SULPHAS. (Mag. Sulph.). $MgSO_4,7H_2O$. **Syn.**—Epsom Salts.—Magnesium Sulphate is prepared by the interaction of magnesium carbonate and sulphuric acid. Contains 99.5 and not more than the equivalent of 102 p.c. of pure magnesium sulphate.

Characters.—Colourless crystals ; odourless. Taste, cool, saline and bitter. Effloresces in warm dry air. *Soluble* in 1.5 parts of water, sparingly soluble in alcohol (90 p.c.).

Incompatibles.—Potassium and sodium carbonates and bicarbonates, lime water, lead acetate, and tartarated soda which preciptates magnesium tartrate.

B. P. Dose.—30 to 240 grs. or 2 to 16 grms.
Enters into.—Mist. sennae co. and Mist. mag. hydrox.

Magnesii Sulphas Exsiccatus. Syn.—*Dried Epsom Salts.*—Exsiccated Magnesium Sulphate is a white odourless powder: taste, saline and bitter. *Soluble* in 2 parts of water, more rapidly in hot water. Contains 62.0 to 70.0 p.c. of $MgSO_4$.

B. P. Dose.—30 to 180 grs. or 2 to 12 grms.

MAGNESII TRISILICAS. (Mag. Trisil.). **Syn.**—"Magsorbent."—Magnesium Trisilicate is prepared by the interaction of solutions of magnesium sulphate and sodium silicate. Contains 30.0 to 32.5 p.c. MgO and 66.0 to 69.5 p.c. SiO_2.

Characters.—In white or nearly white powder; odourless; tasteless; slightly hygroscopic. Insoluble in water.
B. P. Dose.—5 to 30 grs. or 0.3 to 2 grms.

Non-official Preparations

1. **Mistura Magnesii Sulphatis Alba, B. P. C.**—*Syn.—Mistura Alba.*—Mag. sulph. 60 gr., mag. carb. lev. 10 gr., peppermint water q.s. 1/2 oz. *Dose.*—1/2 to 1 oz. or 15 to 30 mils.
2. **Mistura Magnesii Carbonatis Aromatica, B. P. C.**—Light mag. carb. 5 gr., sodium bicarb. 10 gr., aromatic tincture of cardamom 5 ms., water, q.s. 1/2 oz. *Dose.*—1/2 to 1 oz. or 15 to 30 mils.
3. **Pulvis Magnesii Trisilicatis Co., B. P. C.**—Mag. Trisil., Sod. Bicarb., Mag. Carb. Pond., Chalk, each 4 oz. *Dose.*—1/4 to 1 dr. or 1 to 4 grms.

Pharmacology of Magnesium Salts

Internally. **Gastro-intestinal tract.**—Both the oxide and the carbonate are **alkaline,** and neutralise the normal or the excessive acidity of the stomach, and the oxide does this without inducing subsequent hypersecretion. The carbonate sets free carbonic acid which exerts a local sedative influence and provokes subsequent hyperacidity. They act as **antacids.** Being sparingly soluble their antacid action extends down the intestine, where they are converted into soluble and therefore cathartic magnesium bicarbonate. What is unaffected is left insoluble. But the direct effect of magnesium ion is that of depression which is more marked when administered by the intravenous or intramuscular injection or applied to the excised strip of the intestine. Hypertonic solution of magnesium sulphate in the duodenum helps expulsion of bile by causing contraction of the gall-bladder and relaxing the sphincter of the common bile duct. (For action of Magnesium Sulphate, *see* Purgatives).

Blood.—Magnesium salts enter the blood as a chloride or lactate and render the **plasma more alkaline.** If salines are used in concentrated form they draw fluid from the blood and tissues and render the blood more concentrated.

The blood plasma contains about 2 to 3 mg. of magnesium per 100 c.c. of blood and plays an important part in the metabolism of the muscle. The muscle enzymes cannot metabolise sugar in the absence of magnesium.

Nervous system.—Taken by the mouth, magnesium salts have very little systemic effect owing to their slow absorption and rapid elimination. The typical effects of Mg-ion are elicited when the salts are given either intra-

venously or subcutaneously or applied directly to isolated tissues, when they depress the nerves and muscles. Magnesium depresses the central nervous system and acts as a narcotic and anaesthetic. Death takes place from paralysis of respiration. Magnesium ion depresses the heart muscle, and high concentration in the blood which follows its parenteral administration may cause bradycardia, impairment of conduction and eventually stoppage of the heart. Respiration fails before the heart. It reduces the irritability of the intestine and counteracts the effect of physostigmine and barium. On the voluntary muscles it acts like curare. Injected into the spinal canal (5 mils of a 12 p.c. solution), or applied to the nerve trunks (25 p.c.), the sulphate induces anaesthesia resembling cocaine, but more lasting.

Relation to Calcium.—Magnesium interferes with calcium metabolism. Magnesium ion has a marked inhibitory effect on calcification. All the systemic effects of magnesium are antagonised by the use of calcium salts intravenously, which restore the equilibrium between the various ions disturbed by an excess of magnesium. An animal anaesthetised by magnesium will return to consciousness within a few seconds after an intravenous injection of calcium.

Absorption and excretion.—The salts are absorbed very slowly but are excreted rapidly so that when given by the mouth they do not increase the magnesium content of the plasma. The factors which influence absorption of calcium also affect magnesium since the salts of both ions have similar physical properties. Its absorption is enhanced by acid reaction in the duodenum. Normally a concentration of 2 to 3 mg. p.c. is present in the serum and about 80 p.c. of serum magnesium is ionised and diffusible, the remaining portion probably remains combined with protein. They are excreted as chlorides in the urine. When however the kidneys are diseased and elimination is defective, sufficient magnesium may be retained in the body to produce drowsiness and even coma. As a purgative it should be used with caution in nephritis. When given parenterally almost the entire amount is eliminated within 48 hours.

THERAPEUTICS

Externally.—A saturated solution of magnesium sulphate used as a compress relieves pain and acts as a local anaesthetic and has been used in erysipelas, orchitis, arthritis and other inflammatory affections. Morrison recommends dressing of wounds with *Magnesium Sulphate Paste* made by mixing in a warm mortar dry magnesium sulphate 45 grm., glycerin 55 grm., phenol 0.5 grm. The

dressing is left unchanged for three to eight days when profuse discharge of serum takes place, when more wool is used. This acts by osmosis and draws fluid from the wound and prevents growth of aerobic and anaerobic organisms.

Internally.—The oxide, the carbonate and the trisilicate are largely employed as **antacid** and **adsorbent** in acid dyspepsia, heartburn, pyrosis, vomiting, sick headache, or any other complaint attended with acidity. Their antacid property is considerably increased by combining them with sodium bicarbonate and bismuth carbonate, as in the treatment of hyperacidity, gastric and duodenal ulcer and chronic gastric catarrh (*see* page 77). In all these conditions it should be given on an empty stomach in order that the insoluble salts may form a protective coating over the gastric mucosa and neutralise hyperacidity. Because the trisilicate has a prolonged antacid action and does not cause alkalosis, and is a protective and adsorbent, it is preferred in hyperacidity, gastric and duodenal ulcer. As a tasteless, unirritating alkaline laxative, the oxide and the carbonate are often used in combination with rhubarb, as pulv. rhei co., in constipation of children. Mist. mag. carb. aromat. is an agreeable and alkaline laxative in acid dyspepsia accompanied by constipation.

Magnesium sulphate 25 p.c. solution in water and flavoured with syrup of lemon in teaspoonful or more doses (purgation should be avoided) taken every morning in a wine glassful of water helps to empty the gall-bladder in **cholecystitis.**

As **antidotes,** magnesia is used in poisoning by mineral acids, oxalic acid, and the salts of mercury, arsenic and copper, as it forms insoluble compounds with them. In alkaloidal poisoning they hinder the absorption of alkaloids by making the contents of the stomach alkaline. But in order to get these antidotal effects, they must be given in very large doses, which is the only objection. Magnesium sulphate acts as an antidote to lead and barium salts by precipitating their insoluble sulphates.

As a **diuretic** and feeble alkaliser of blood and urine, they are used in gout and gravel cases, where the salts of potassium and sodium are not well borne. Many mineral waters containing magnesium are valuable diuretics, such as Harrogate, Carlsbad, Ems, Baden-Baden, etc.

For its paralysing effects on the nerve tissue the sulphate has been used as intraspinal injection in **tetanus** (3 to 4 mils of a 25 p.c. solution), and for the production of **spinal anaesthesia.** In tetanus it relieves spasms but does not cure. Similarly intravenous injections of 10 to 25 mils (150 to 375 ms.) of a 10 p.c. solution have been

used to relieve spasms of **eclampsia.** This is followed by 5 to 10 ms. of 25 p.c. solution intramuscularly after each convulsion, until controlled. It has also been used hypodermically in chorea and epilepsy and to reduce **intracranial pressure,** when concentrated solution has been used per rectum (3 to 6 oz. in water). In the treatment of chorea of children of 4 to 5 years, 3 to 5 ms. of a 25 p.c. aqueous solution is given as injection deep into the buttocks every 2 days, and for older children 10 ms. Improvement generally occurs after 2 to 5 injections. Because of its narcotic property, it has been recommended (intramuscularly 0.25 grm. per kilo) as a preliminary to ether anaesthesia, when it reduces the minimal concentration of ether required to produce general anaesthesia. As an enema, or intravenously (2 mils of a 50 p.c. solution), it is valuable in headaches following spinal anaesthesia. The *margin of safety* between the effective therapeutic dose and the toxic dose being small this restricts its use, as it paralyses the respiratory centre when used in large therapeutic doses.

Note.—For injection the solutions should be sterilised in an autoclave.

BARII SULPHAS

Barium Sulphate. $BaSO_4$

Source.—Prepared by the interaction of a soluble barium salt and a soluble sulphate.

Characters.—A heavy white, amorphous powder. No odour, or taste. Stable in air. *Insoluble* in water, slightly soluble in hydrochloric and nitric acid.

Non-official Preparations

1. **Pulvis Barii Sulphatis Compositus, B.P.C.** *Syn.—Barium Meal*; *Shadow Meal.*—Barium sulphate 10 oz., saccharin 1 gr., vanillin 3 gr. *Dose.*—4 to 8 oz. or 120 to 240 grm., mixed immediately before use with a sufficient quantity of water.
2. **Barii Chloridum.**—Colourless crystalline plates, soluble in 2.5 parts of water. *Dose.*—1/2 to 2 grs. or 0.03 to 0.12 grm. Maximum single dose 3 grs.

Action and Uses

Barium belongs to the group of alkaline earths but is more poisonous. The soluble salt (chloride) is absorbed with difficulty from the intestine but sufficiently to produce systemic effect. The chief action is exerted on all forms of muscular tissue which are powerfully stimulated, *e.g.* those of the intestine, bladder, vessels and bronchi. Owing to the vaso-constriction it causes a rise of blood pressure. It increases the excitability of the heart, slows the rate and improves its tone, resembling digitalis effects; and at one time was suggested as a substitute for that drug. In practical therapeutics, however, it has not come up to the expectations made of it, although its use has been suggested in syncope of heart block.

Sulphate of barium is insoluble and passes through the body unchanged, and being opaque to X-rays is used in preference to bismuth as a contrast meal in X-ray examination of the alimentary canal, either by the mouth or per rectum. Two to 5 ounces are generally required, and are given mixed with cornflour, kaolin and malted milk, or in the form of *shadow meal.* Atropine (1/60 gr. or 1 mg.) is a valuable adjuvant specially for visualisation of the

appendix for which object it is given as an enema one hour before barium. Barium however is inferior to bismuth, which, owing to its high molecular weight, gives a darker shadow.

Caution.—As accidental deaths have taken place by the use of poisonous *barium sulphide* when the sulphate has been prescribed, the physician should be careful in writing the prescription in full, without abbreviation, and should satisfy himself before allowing the patient to take the drug. It is always safe to order some special preparation intended for X-ray examination only.

Baryta Sulphurata. *Syn.—Sulphide of Barium.*—It is a caustic and poison, and it is used as a **depilatory** to remove superfluous hairs, mixed with wheat starch in the proportion of 1 to 3. Make a paste with water and apply on the part and scrape off with a blunt knife after five to ten minutes.

GROUP II : ACIDS

Acid Acetic, Trichloracetic, Citric, Tartaric, Hydrochloric, Nitric, Sulphuric, Phosphoric, Hypophosphorous, Lactic.

ACIDUM ACETICUM GLACIALE. (Acid. Acet. Glac.). $CH_3.CO_2H$.
Glacial Acetic Acid is obtained by the action of sulphuric acid on an acetate, or by synthesis. Contains not less than 99 p.c. of acetic acid.

Characters.—A clear, colourless liquid with pungent odour. Miscible with water and most fixed and volatile oils.
Enters into.—Liq. ammon. acet. fort. and dil.

Acidum Aceticum. (Acid. Acet.).—Acetic Acid. Contains 33 p.c. of acetic acid.

Characters.—A clear, colourless liquid with a pungent odour. Taste, sharply acid.

Official Preparations

1. **Acidum Aceticum Dilutum.—6 p.c. of acetic acid. It is an ingredient of acet. scill. and tinct. ipecac.**
2. **Oxymel.—15 p.c. acetic acid. B. P. Dose.—30 to 120 ms. or 2 to 8 mils.**

Pharmacology and Therapeutics

Externally.—Glacial acetic acid is a **caustic** and being volatile spreads beyond the area of application. It is used for destroying corns and warts. It speedily vesicates and may be used in those cases where cantharidin cannot be employed, but it causes much pain, and if not cautiously applied, may produce a nasty sore.

Acetic acid destroys tinea, and is an effective application for ringworm. Vinegar, or diluted acetic acid, is used as an **external refrigerant** in cerebral congestion, sprains and bruises ; and sponging with vinegar will reduce pyrexia and check excessive sweating.

Internally.—Dilute acetic acid allays thirst by increasing the salivary secretion, and may be used as a gargle (15 ms. to 1 oz.) in cases where dryness of the mouth is a troublesome symptom. In the duodenum it is converted into acetate by the alkaline secretion which after absorption is converted into bicarbonate in the tissues and excreted as such, rendering the urine less acid or even alkaline.

ACIDUM TRICHLORACETICUM. (Acid. Trichloracet.). $CCl_3.CO_2H$.

Trichloracetic Acid is prepared by the oxidation of chloral with nitric acid. Contains not less than 9[illegible] p.c. of trichloracetic acid.

Characters.—Colourless, very deliquescent crystals, or crystalline masses, with a characteristic pungent odour. *Soluble* freely in water (9 in 1), in alcohol (90 p.c.) and in solvent ether. **Should be kept in well closed containers.**

Action and Uses

Trichloracetic acid is a caustic, less painful than nitric acid. A weak solution is useful in stimulating granulating surface and for washing wounds and ulcers, specially phagedaenic ulcers of the cheek. As a caustic the pure acid liquefied with minimum of water is used in warts and to cauterise venereal and other sores. Mixed with glycerin (1 in 2) it is used in chronic pharyngitis.

It forms a delicate test for albumin in urine ; a few drops of saturated solution added to the urine slowly forms a white cloud at the junction of the two fluids.

ACIDUM CITRICUM. (Acid. Cit.). $C_6H_8O_7,H_2O$.—Citric Acid is obtained from lemon juice, or may be prepared from glucose.

Characters.—Large, colourless crystals, or a white powder ; slightly hygroscopic in moist air, and slightly efflorescent in dry air ; odourless. Taste, strongly acid. *Soluble* in less than 1 part of water, in 1.5 parts of alcohol (90 p.c.).

20 grs. of Citric Acid in 1 oz. of water	will neutralise	28.5 grs of Pot. Bicarb. 24 grs. of Sod. Bicarb. 15 grs. of Ammon. Carb.

B. P. Dose.—5 to 30 grs. or 0.3 to 2 grms.

ACIDUM TARTARICUM. (Acid. Tart.). $C_4H_6O_6$.—Tartaric Acid is prepared from potassium acid tartrate.

Characters.—Colourless crystals, or a white powder ; odourless ; taste, strongly acid. *Solubility.*—In less than one part of water, and in 2.5 parts of alcohol (90 p.c.).

Incompatibles.—Salts of calcium, potassium, lead, mercury, alkalies, carbonates and vegetable astringents.

20 grs. of Tartaric Acid in 1 oz. of water	will neutralise	27 grs. of Pot. Bicarb. 22 grs. of Sod. Bicarb. 15 grs. of Ammon. Carb.

B. P. Dose.—5 to 30 grs. or 0.3 to 2 grms.
Enters into.—Pulv. Efferv. Co., Inj. Adrenalinae.

Pharmacology and Therapeutics of Citric Acid and Tartaric Acid

Internally.—These acids unite with the bases to form neutral salts. When given in an effervescing form combined with bicarbonate of soda, the liberated carbonic acid gas acts as gastric sedative. therefore effervescing mixtures are used to check nausea and vomiting ; the tartrates and citrates formed act as saline purgative, as Pulvis Effervescens Co. Because they stimulate salivary secretion, they are used as refrigerent drinks in the form of lemonade to allay thirst in fevers.

When added to drawn blood citric acid retards clotting by combining with calcium and forming a non-ionisable salt. Given by the mouth no such effect is observed. They are converted into neutral salts in the alimentary canal and are oxidised after absorption, *e.g.* potassium citrate is converted into potassium bicarbonate, carbonic acid and water, thereby increasing the alkalinity of the plasma.

Urine.—They are eliminated as carbonates thereby increasing the alkalinity of the urine, except when given in large doses when they escape unchanged.

ACIDUM HYDROCHLORICUM. (Acid. Hydrochlor.). Syn.—Muriatic Acid; Spirit of Salt.—Hydrochloric Acid is obtained by dissolving hydrogen chloride in water. Contains 35.0 to 38.0 p.c. w/w of HCl.

Characters.—A colourless, strongly acid liquid emitting white fumes. Odour, pungent.

Incompatibles.—Lead and silver salts, alkalies and their carbonates.

OFFICIAL PREPARATION

1. **Acidum Hydrochloricum Dilutum.**—Contains 10 p.c. w/w of hydrogen chloride. **B. P. Dose.—10 to 120 ms. or 0.6 to 8 mils.**

ACIDUM NITRICUM. (Acid. Nit.).—Nitric Acid is prepared by the interaction of sulphuric acid and sodium nitrate; containing 70 p.c. w/w of HNO_3.

Characters.—A clear, colourless, acid liquid, emitting corrosive fumes.

Incompatibles.—Alkalies, alcohol, carbonates, oxides, sulphides, oxidisable substances, iron sulphate and acetate of lead.

Enters into.—Ung. Hydrarg. Nit. Fort. and Dil.

NON-OFFICIAL PREPARATION

1. **Acidum. Nitro-hydrochloricum Dilutum, B. P. C.**—Contains about 12.5 p.c. w/w of nitric acid and 13.5 p.c. w/w of hydrochloric acid. *Dose.*—5 to 20 ms. or 0.3 to 1.2 mils.

PHARMACOLOGY AND THERAPEUTICS

Externally.—Being a powerful **caustic,** strong nitric acid is employed to destroy chancres, warts, haemorrhoids, phagedaenic sores and the poison of venomous snakes and rabid dogs. Owing to the formation of nitro-derivatives of tyrosine it stains the skin yellow. Applied diluted (5 to 10 mils in a bowl of water) it hardens the skin and prevents excessive sweating. As a bath nitro-hydrochloric acid is useful in chronic hepatic congestion (*see* page 41).

Internally.—Hydrochloric acid being the normal acid of the gastric juice aids transformation of the pepsinogen into pepsin and helps digestion of proteins. In the duodenum, acids reflexly excite the flow of pancreatic juice and govern the production of the hormone secretin. Since the entrance of secretin into the blood stream stimulates the formation of bile, hydrochloric acid also acts indirectly as a cholagogue. These acids are therefore used in gastric disorders, preferably with nux vomica or some bitter.* As a **stomachic** they are given freely diluted before meals. In fermentative dyspepsia due to the absence of the antiseptic action of the gastric juice, and in other conditions arising from a deficiency of the acid, they are given after food. Given towards the end of gastric digestion they are useful in intestinal catarrh and chronic diarrhoea. They are also used to reduce the alkalinity of the urine in phosphatic deposits and to stimulate the hepatic action. Owing to the deficiency of the normal gastric juice so common in pernicious anaemia, hydrochloric acid has been used in its treatment in 20 to 30 ms. doses, freely diluted. For the same reason it is used in typhoid fever.

* Acid. Hydrochlor. Dil.		ms.	15
Sp. Chlorof.		ms.	15
Tinct. Nuc. Vom.		ms.	10
Inf. Gent. Co.	ad.	oz.	1

To avoid irritation of the throat and stomach, acids should be given freely diluted, and taken with a glass tube or quill to prevent their action on the teeth.

Acids are contra-indicated in catarrhal conditions of the stomach with excessive accumulation of mucus. Prolonged administration in large doses even in normal persons causes irritation and indigestion.

ACIDUM PHOSPHORICUM. (Acid. Phosph.).—Phosphoric Acid. Contains 89.0 p.c. w/w of H_3PO_4.

Characters.—A colourless, syrupy liquid; taste and reaction acid. Miscible with water.

Incompatibles.—Alkalies, carbonates, ferric chloride, lead salts and calcium salts.

Enters into.—Syr. Ferr. Phosph. Co.

Official Preparation

1. **Acidum Phosphoricum Dilutum.**—10 p.c. w/w of phosphoric acid. **B. P. Dose.—5 to 60 ms. or 0.3 to 4 mils.**

Pharmacology and Therapeutics

Internally.—The diluted acid is a refrigerant. It does not derange the digestion and makes an agreeable drink in diabetes and febrile diseases. By some it is considered serviceable in cases of hypophosphaturia. It has no virtues of free phosphorus.

ACIDUM HYPOPHOSPHOROSUM DILUTUM. (Acid. Hypophosph. Dil.).—Dilute Hypophosphorous Acid. Contains 10 p.c. w/w of H_3PO_2.

Characters.—A clear, colourless liquid; odourless; taste, strongly acid. Miscible with water and with alcohol (90 p.c.).

B. P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

Uses.—It has the same action as other acids and being a powerful reducing agent is added to Syr. Ferri Iodidi as a preservative. It is used in the form of hypophosphites, or as Syr. Hypophosph. Co.

Acidum Sulphuricum Dilutum. B. P. C. (Not official).—Sulphuric acid 104 and distilled water 896. Dose.—5 to 60 ms. or 0.3 to 4 mils.

Acidum Sulphuricum Aromaticum. (Not official). *Syn.—Elixir of Vitriol.*—Sulphuric acid 70 mils, tincture of ginger 250 mils, sp. cinnamom. 15 mils, alcohol (90 p.c.) to 1000 mils. *Dose.*—5 to 20 ms. or 0.3 to 1.2 mils.

Uses.—Sulphuric acid prevents absorption of lead by forming an insoluble sulphate, and therefore lemonade made with sulphuric acid is largely used by workers in lead factories as a prophylactic against plumbism. Acid. sulph. aromat. is used in the treatment of diarrhoea and early stage of cholera.

General Pharmacology of Acetic, Citric, Tartaric, Hydrochloric, Nitric, Phosphoric, Hypophosphorous and Sulphuric Acids

All these acids owe their property to the presence of hydrogen-ion. They neutralise alkalies, and in concentrated solution have a strong affinity for water, and coagulate proteins. The hydrogen-ion in organic acids, e.g. citric acid, is less dissociable and are therefore less powerful than the inorganic acids, where the hydrogen-ion is easily dissociated. Other acids like salicylic, benzoic, hydrocyanic, behave in the same way as their salts.

Acid solutions check the automatic movement of plain muscles and diminish the height of contraction to electrical stimulation of the striped muscle. These effects on the isolated organs are proportional to their power of dissociation, and can be checked by neutralising the acid by an alkali. Since most living matter is neutral or slightly alkaline, acids are protoplasmic poisons.

Externally.—In concentrated form acids are powerful **irritants** and **caustics**, and by penetrating into the skin and subcutaneous tissues cause severe pain and necrosis, and if extensive, produce symptoms of shock and collapse. Hydrochloric acid is less destructive, while concentrated organic acids are still less so, but may cause blisters and are only caustics. Dilute solutions, specially sulphuric acid, are local astringents and styptics. The organic acids, freely diluted, act as refrigerants and anhydrotics.

Internally. **Alimentary canal.**—The corrosive action of the concentrated acids is more marked when applied to a mucous surface. Thus when swallowed they cause severe burning and destruction of the mucous membrane of the mouth, oesophagus, stomach, etc., followed by severe shock, collapse and death. Recovery rarely takes place, but it is always accompanied by contraction due to cicatrix formation, difficulty in deglutition and eventually death from inanition.

Diluted acids have a peculiar sour taste and are mild astringents. They soften the enamel of the teeth and reflexly increase salivary secretion and allay thirst. In the stomach they neutralise free alkali and form neutral salts. Since pepsin acts in the presence of free acids, acids, specially hydrochloric acid, play an important part in the digestion of proteins. Acids also act as an antiseptic. The presence of free acid in the stomach increases pyloric peristalsis, closes the cardiac and opens the pyloric sphincters, while its presence in the duodenum causes reflex closure of the pylorus which does not open till the contents have been neutralised by the intestinal juices. Excessive acidity therefore by retarding neutralisation in the duodenum delays opening of the pyloric sphincter and prolongs the period of digestion in the stomach. Acids also help the formation of secretin which in its turn increases pancreatic secretion.

Blood and tissues.—Acids are rapidly absorbed and circulate as salts formed by neutralising the alkalies of the body. They therefore reduce the alkalinity of the blood, and if the acids are absorbed in large quantities, sufficient to neutralise the fixed alkalies of the body, the alkalinity of the blood is so reduced that the animal dies of acidosis. This however is only possible in herbivorous animals, while in carnivorous animals and in man, the fixed alkalies are

spared by the neutralisation of the acids by ammonia (*see* Acidosis).

Kidneys.—Acids are eliminated as neutral or acid salts, and as a result of salt action act as diuretics. But the urine is rendered more acid from the formation of acid salts which may cause irritation of the kidney and the genito-urinary mucous membrane. Nitric acid is partly converted into ammonia and tends to increase the alkalinity of the blood. The organic acids, viz., acetic, citric and tartaric, are oxidised in the body into carbonates and make the urine alkaline.

Acute toxic action.—All these acids are **irritant poisons.** If swallowed in a concentrated form, intense burning pain extending from the mouth to the stomach, excoriation, and formation of grey or yellowish eschar in the mouth, severe abdominal pain and tenderness, vomiting of coffee-coloured matter containing dark clots of blood and shreds of mucus, constipation, or if bowels are open, stools dark from the admixture of blood are the prominent symptoms. Dyspnoea due to laryngeal swelling, either from irritant fumes or from the introduction of some of the acid, is not infrequent. Collapse with cold perspiration soon sets in and the patient dies.

Antidotes.—No *pump.* Mild alkalies, such as lime water, magnesia in a moderately diluted solution, or soap. Demulcents, or egg albumin, bland oils, linseed tea, etc. Morphine subcutaneously to relieve pain ; etc. Carbonates and bicarbonates should not be used.

ACIDUM LACTICUM. (Acid. Lact.). $CH_3CHOH.CO_2H$.—Lactic Acid is obtained by the lactic fermentation of sugar.

Characters.—A colourless, or slightly yellow, syrupy liquid ; hygroscopic, inodorous. *Solubility.*—Freely in water, alcohol (90 p.c.), and in solvent ether.

Official Preparation

1. **Injectio Sodii Lactatis Composita.** *Syn.—Hartmann's Solution for Injection ; Ringer-Lactate Solution.*

Pharmacology and Therapeutics

Externally.—The concentrated acid is corrosive and is used alone or in the form of a paste with kaolin to destroy lupus. A lotion (1 p.c.) is used to wash abscess cavities. Because of its low toxicity, it is used as a mild antiseptic and caustic for mucous surfaces, and a 10 p.c. solution is used as a douche in leucorrhoea ; while in the form of a jelly or pessary containing 1 to 2 p.c. of the acid with boric acid it is used as a contraceptive.

Internally.—A 10 to 50 p.c. solution in glycerin has been successfully applied to pharyngeal tubercles after scraping, the strength is slowly increased till pure acid is used. As a pigment or spray it is occasionally used to dissolve false diphtheritic membranes. On the stomach it acts like hydrochloric acid and is often given as a gastric adjuvant in dyspepsia. It is considered to be a valuable intestinal disinfectant, specially of the large bowel, and is useful in the diarrhoea of phthisis, of enteric fever, and in the green diarrhoea of infants. The usual practice is to give $7\frac{1}{2}$ ms. three times a day after food. Infants thrive

better on milk to which lactic acid has been added in the proportion of 60 ms. to 1 pint. It enters the blood as a lactate, and is eliminated in the urine as a carbonate.

Soured milk prepared by adding lactic acid bacillus (*B. bulgericus*) has been used in the treatment of diseases of the large bowel, colitis, chronic dysentery, etc., and also in the summer diarrhoea of infants. It acts by changing the flora of the intestine which inhibits the growth of putrefying organisms.

Ringer-Lactate solution is used intravenously in doses of 30 mil. per kilo of body weight prior to chloroform anaesthesia to prevent possible acidaemia. It provides an antiketogenic substance (glucose) by synthesis, and yields on oxidation sodium bicarbonate in the body and is used intravenously to overcome acidosis such as that of diabetes. It has also been used in the treatment of dehydration.

GROUP III
HEAVY METALS

Although some of the metals in this group are not heavy it is convenient to group them together since they have many properties in common, but individually they have some important actions and therapeutic uses of their own. For instance, mercury is *antisyphilitic*, iron *haematinic*, while others are more or less *astringents* and *caustics*. In the form of pure metals they have practically no action, except a mechanical one, but become active only when they are capable of dissociation into ions. Iron and mercury are the only metals that are used in the pure form, all others are used either as organic or inorganic compounds. The more completely dissociated the ions of the salts are, the more rapid and more intense is the action. Thus the inorganic salts are more active than the organic preparations and double salts, which are less readily ionised.

The soluble salts precipitate proteins and form albuminates of variable composition and the acids with which these metals are combined are liberated. As a rule the acid ion is more important for the local action than the metal. The chlorides and nitrates are dissociated more rapidly and are corrosives, the sulphates are dissociated less rapidly and are less irritant, while the acetates, tartrates and citrates are least corrosives as they are very slowly dissociated. The double salts do not precipitate proteins and have therefore very little astringent effect. In concentrated solutions the precipitate extends into the cells and may have an irritant or even a caustic effect, causing death of the tissues. All these salts therefore are astringents, irritants and caustics, according to the strength and preparation used. This astringent action

resembles that of the vegetable astringents (q. v.) which also act by precipitation of proteins.

When used by the mouth they also act as astringent to the alimentary canal, and some specially lead is constipating, while mercury acts as a purgative, and zinc and copper act as emetic.

The salts of the heavy metals are very slowly absorbed and slowly excreted, and are therefore more or less cumulative. Chronic poisoning by some of the metals may follow the repeated use for a long time even if the dose be very small. Mercury, however, is the only metal that is absorbed freely from the alimentary tract. They are mostly stored up in various organs, chiefly the liver, the spleen, the kidneys and the bone-marrow. Except mercury, excretion of these metals *via* the kidneys is less. In large doses they may produce nephritis. The nervous system is sensitive to these metals. Disturbances of psychical centres, delirium, mania, peripheral neuritis, and sclerosis of the brain and cord are some manifestations of poisoning from heavy metals.

Many salts of heavy metals are powerful disinfectants, perchloride of mercury is however extensively used as such. Their action is due to the precipitation of the proteins of the microbes, and a specific poisonous action on the bacteria themselves. The action of mercury is complex ; the metal is first adsorbed upon the surface of the bacteria and then enters and kills the bacteria. It therefore takes a longer time to act and will produce its germicidal action even in low concentration provided sufficient time is given. Naegeli has found that some metals in infinitesimal quantities kill algae, infusoria and bacteria, which has been termed *oligodynamic action* of the drug. In practical therapeutics this oligodynamic action is produced by the colloidal metals. As these are not dissociated into ions they are not irritants, but the free ions formed are pharmacologically active ; although not powerful enough to produce any local irritation they have a powerful bactericidal effect in very dilute solutions.

Colloidal Metals.—Since the vital processes of the body fluids and living tissues are colloidal pheonomena, it has been suggested that if therapeutic agents could be administered in colloidal form they will react with the body tissues where colloidal conditions prevail. A substance is said to be in colloidal state when its particles are sufficiently finely divided in sub-microscopic size as can be kept in solution without mechanical suspension. Colloidal solutions resemble true solutions in so far that the particles remain in suspension and do not form deposit as happens when a mechanical suspension is made. The particles in colloidal solution do not separate out in the liquid owing

to Brownian movement and to the electric charges which they carry. In some this charge is positive, but in the majority it is negative, and the mutual repulsion of similarly charged particles keep them in suspension. Colloidal metal is obtained by passing an electric arc between metallic wires under water, when the metal remains evenly and permanently distributed in the solution in very fine subdivision. The metal exists in non-ionisable form and therefore does not cause any irritation, and is physiologically inactive, but becomes active by slowly passing to the ionic form by the action of bacteria. They have been credited of possessing certain properties in common with ferments.

The use of colloidal solutions in medicine is based on the fact that the minute particles remaining in solution give a larger surface area and therefore confer greater activity. Thus colloidal kaolin, owing to larger surface area, possesses a greater adsorptive power than ordinary kaolin. Colloidal metals have been extensively used as internal antiseptics in many forms of infections, chiefly puerperal and other septicaemias, but with doubtful results. Colloidal silver has been used in many septic conditions and infections. They are used hypodermically and even intravenously. The injections are followed by a rise of temperature (sometimes hyperpyrexia) and leucocytosis. Their gradual transformation into the ionic form elicit the typical action of the metal.

The heavy metals are classified as follows :—

Class A : Antisyphilitic and antiseptic : **Mercury**
Class B : Haematinic : **Iron**
Class C : Astringents : **Lead, Silver, Zinc, Copper, Alum**
Class D : Anti-tubercular : **Gold**
Class E : Depilatory : **Thallium**

Of these **Mercury** and **Gold** will be discussed with other Chemotherapeutic Agents, and **Iron** with Drugs Acting on the Blood.

1. Astringent Metals

Lead, Silver, Zinc, Copper, Alum

PLUMBI ACETAS

(Plumb. Acet.). $Pb(CH_3.CO_2)_2,3H_2O$

Syn.—Sugar of Lead.

Source.—Lead Acetate is obtained by the interaction of lead oxide and acetic acid.

Characters.—Small, white, transparent monoclinic prisms, or heavy crystalline masses ; slightly efflorescent ; odour, acetous ; taste, sweet, astringent. *Solubility.*—1 in 2.5 of water, 1 in 30 of alcohol (90 p.c.).

Incompatibles.—Mineral and tannic acids and their salts, alkalies, lime water, chlorides, iodides, preparations of opium, mucilage of acacia, albuminous fluids and hard water.

B. P. Dose.—1/2 to 2 grs. or 30 to 120 mg.

Liquor Plumbi Subacetatis Fortis. (Liq. Plumb. Subacet. Fort.). Syn.—Goulard's Extract.—Strong Solution of Lead Subacetate is prepared by dissolving lead acetate in water, adding lead monoxide ; filtering and washing.

Characters.—A clear, colourless alkaline liquid, becoming turbid from exposure ; taste, sweet, astringent ; reaction alkaline. Contains 19.0 to 21.5 p.c. Pb.

OFFICIAL PREPARATION

1. **Liquor Plumbi Subacetatis Dilutus.** *Syn.—Goulard's Lotion ; Goulard Water.*—1.25 p.c. strong liquor.

PLUMBI MONOXIDUM. (Plumb. Monox.). Syn.—Litharge ; Plumbi Oxidum ; *Mudra sung*, Beng.—Lead Monoxide is prepared by the oxidation of molten lead.

Characters.—Pale brick-red, or pale orange, heavy scales or powder. *Solubility.*—In dilute nitric acid, acetic acid and in warm solutions of alkali hydroxides ; almost insoluble in water.

Enters into.—The preparation of Liq. Plumb. Subacet. Fort.

NON-OFFICIAL PREPARATIONS

1. **Pilulae Plumbi cum Opio, B.P.C.**—Lead acetate 40 grs., opium 6 grs., syrup of glucose q.s. for 25 pills. *Dose.*—1 to 2 pills.
2. **Lotio Picis Carbonis et Plumbi, B.P.C.**—Solution of coal tar, 300 ms. ; strong solution of lead subacetate, 300 ms. ; distilled water, q.s. 20 oz.
3. **Unguentum Plumbi Oleatis.** *Syn.—Diachylon Ointment ; Hebra's Ointment.*—Lead plaster 50, ol. lavender (by weight) 1, olive oil (by weight) 49, melt with heat. Useful in *eczema* and *sycosis.*

PHARMACOLOGY OF LEAD SALTS

Externally.—Lead salts have a feeble action on the unbroken skin, but on the denuded surface and exposed mucous membrane, wound and ulcer, they produce precipitation of discharges and form an impervious coating on the surface. Since the metal contained in the precipitate has no destructive effect on the cells it is not corrosive ; on the other hand it has a sedative action and allays itching. It coagulates the albumin of the tissues. Lead therefore is an **astringent, antiphlogistic** and **local sedative.**

Internally.—Insoluble lead salts have no taste, the soluble salts are astringent and sweetish. They have the same local action in the mouth, stomach and intestine as on the skin, and are converted into an albuminate and absorbed as such. The unabsorbed portion is eliminated by the stool as sulphide colouring it leaden black. They cause constipation and stop haemorrhage from the intestine. The action is due to retardation of peristalsis and a diminution of secretion due to astringent action.

Absorption and elimination.—Lead salts enter the blood from the alimentary canal, skin, and the respiratory tract. Lead enters the blood more rapidly than any other heavy metal except mercury, and being excreted slowly, it is apt to accumulate in the body. Because of its slow absorption, large single doses do not produce any symptoms of poisoning, but minute doses slowly absorbed for a prolonged period give rise to symptoms of chronic poisoning. The central nervous system, kidneys, liver and the bone are the principal organs where it is deposited. It is excreted slowly by the urine, bile, sweat, milk and the faeces.

The action is best studied from cases of *chronic poisoning.*

The symptoms are characteristic, and involves the nutrition and

the condition of the blood. Loss of appetite, nausea, impaired digestion, obstinate constipation, a sweet metallic taste in the mouth, intestinal colic (lead colic) and formation of a *blue line on the edges of the gums* are the early symptoms. The blue colouration is due to deposit of lead sulphide in the subepithelial tissue and cannot be removed by rubbing. This is formed when lead in circulation comes in contact with the hydrogen sulphide formed by putrefaction around unclean and carious teeth, and does not occur if the teeth and mouth are kept clean.

Lead colic may sometimes be very severe, and is due to spasm of the intestine. The cause of this is not definitely known, although it has been suggested as being the result from spasmodic contractions of the localised circular muscles only. Therefore no purgation follows; on the contrary there is severe constipation. Some however hold that the contraction is due to vascular spasm, and is relieved by amyl nitrite.

Anaemia is common and is sometimes the only symptom. It may be due to malnutrition but mainly to destruction of red blood corpuscles, and the changes in red bone marrow are secondary to anaemia. A very characteristic condition of the blood is the appearance of basophilic stippling. There is an increase of leucoblastic cells with disappearance of fat, followed by gelatinous degeneration and atrophy. **Leucocytosis** is common.

The effect on the uterine muscle is responsible for **dysmenorrhoea, amenorrhoea, menorrhagia,** and **abortion** in pregnant women, and for this reason lead plaster is often administered with criminal intent. Peripheral vessels become powerfully constricted resulting in arteriosclerosis and high blood pressure. This at one time was thought to be reflex from pain, but since it is permanent and remains after the subsidence of pain, which is spasmodic, it must be the result of direct action on the arterial muscle. In the same way the heart muscle is also affected although the actual amount of work done is not increased.

Severe cramps of the leg next appear followed by paralysis of the extensors of the forearm, leading to **wrist drop** from chronic peripheral neuritis of the motor nerves supplying the muscles. The affected muscles become the seat of fatty degeneration, but it is to be noted that the supinator longus escapes. The paralysis may extend to other muscles and there may be paraplegia or hemiplegia.

Arthralgia occurs in certain percentage of patients. The symptoms are sudden paroxysmal attacks of violent pains, generally at nights, and disturbed functions of joints and groups of muscles, specially those of the shoulder and the flexors. These attacks resemble gout and are possibly due to deposition of lead phosphate about the joints, or may be neuralgic, neuritic or central.

Occasionally marked cerebral symptoms are seen leading to lead **encephalopathy**. The onset may be gradual or sudden with vertigo, violent headache, tinnitus, strabismus and other cerebral manifestations like stupor, weakness and tremors. Saturnine lunacy and saturnine epilepsy may result from the action of the poison on the nervous centres. Also optic neuritis and blindness (**lead amblyopia**). This may be the sequence of albuminuric retinitis or effusion into the optic sheath.

As lead prevents excretion of urates from the blood, gouty inflammation of joints often ensues, specially in patients with a gouty diathesis. Chronic lead poisoning is also a common cause of granular kidney with all its attendant symptoms.

Tetra-ethyl of lead is used with petrol, but gives rise to highly poisonous and toxic fumes. It is freely absorbed by the lungs and skin. The symptoms are the same as those of lead.

Treatment.—Conditions favouring calcium retention help storage of lead in the bones, and therefore calcium lactate, or milk (because

of its high calcium content) should be given during the acute symptoms to help deposition of lead in the bone. After the acute symptoms are over efforts should be made to help excretion by maintaining a negative calcium balance by low intake of calcium, by giving acid, like phosphoric acid, or ammonium chloride and parathormone. Atropine, morphine and nitrites to relieve colic and constipation. Potassium iodide to dissolve insoluble compounds of lead and magnesium sulphate to remove them from the system, and prevent their reabsorption after they have been eliminated into the intestine. Sulphur baths to help elimination by the skin; lumbar puncture in encephalopathy.

Therapeutics of Lead Salts

Externally.—Generally speaking, lead salts are useful in variety of diseases :—(1) To *soothe irritation and control excessive discharge*, the lotions and ointments are employed in inflamed, painful, weeping eczema, irritable ulcers and wounds. The lotion may be used in vulvitis, leucorrhoea, otorrhoea, etc. A lead and opium lotion* is a good sedative application to bruises, sprains and other cutaneous inflammations. Diachylon ointment, alone or combined with zinc oleate or mercuric oleate ointments, makes a very effective non-irritant application. (2) To *allay irritation and itching*, a lotion or ointment is used in pruritus pudendi (the cause being first removed), urticaria, etc. †

Internally.—For its local astringent effects, Glycerinum Plumbi Subacetatis (strong solution of lead subacetate 5, glycerin 5, water q.s.), or a gargle can be used in tonsillitis, pharyngitis, etc. Lead acetate is the only salt that is used internally. Its chief use is to check severe diarrhoea and haemorrhage from the stomach and bowels as in typhoid fever and tuberculosis. Pilulae plumbi c. opio is a useful preparation in such cases. Lead suppository or an enema of acetate of lead may be employed to arrest rectal haemorrhages.

ARGENTI NITRAS

Silver Nitrate. (Argent. Nit.). $AgNO_3$

Syn.—Lunar Caustic.

Source.—Prepared by the action of nitric acid on silver.

Characters.—Colourless, tabular crystals. Taste, bitter, metallic. *Solubility.*—In 0.5 part of water.

Incompatibles.—Alkalies and their carbonates, bromides, chlorides, phosphates, iodides, acids (except nitric and acetic), alkaloids, and solutions of arsenic and tannin.

Official Preparation

1. **Argenti Nitras Induratus.** *Syn.—Toughened Caustic.*—Greyish white, or white cylindrical rods or cones. Freely soluble in distilled water and sparingly soluble in alcohol (90 p.c.). Obtained by fusing silver nitrate 95 parts and potassium nitrate 5 parts and pouring into moulds.

*Tinct. opii	ms. 10
Liq. plumb. subacet. dil.	ms. 60
Aqua	ad. oz. 1

†Calamine	oz. 3
Glycerin	oz. 1
Liq. plumb. subacet. dil. ad.	oz. 20

ARGENTOPROTEINUM. (Argentoprot.). **Syn.**—Argentum-Proteinicum Forte; Strong Silver Protein; "Protargol".—Silver Protein is a compound of silver and protein. Contains 7.5 to 8.5 p. c. of Ag.

Characters.—A brown powder; odourless; somewhat hygroscopic. Slowly soluble in about 2 parts of water, forming a dark brown solution; almost insoluble in alcohol (95 p.c.).

N.B.—It should be kept in well-closed container, protected from light, and the solution should be dispensed in amber-coloured bottles.

Non-official Preparations

1. **Argentum Colloidale** (Crede's), *Syn.—Collargol.*—Metallic silver in a colloid state. Its ointment (Agent. Coll. 15, Cera Alba 10, Adeps Benz. 75) is used as a prophylactic to *gonorrhoeal ophthalmia.*

2. **Argentum Proteinicum Mite, U.S.P.** *Syn.—Argyrol; Mild Protargin.*—Silver rendered colloidal by the presence of, or combination with protein. Contains 19 to 25 p.c. silver. Dark brown or almost black shining scales or granules. Very soluble in water, but not in alcohol. An excellent non-irritating application for mucous membranes. In *colitis,* 1 p.c. solution as enema. For *cystitis* use 1 in 5000 solution. As a mild caustic 1 in 100. In ophthalmic practice as a *prophylactic* against ophthalmia neonatorum 25 p.c. In *gonorrhoea* as a prophylactic, 10 p.c.; urethral irrigation 1 in 1000. Bowel wash, 0.1 to 1 p.c.

3. **Albargin.** *Syn.—Silver Gelatose.*—Contains 15 p.c. of silver. A 0.2 p.c. solution useful as an injection in *gonorrhoea.* A 0.25 p.c. solution as a bowel wash in dysentery.

Pharmacology of Silver Salts

Externally.—Soluble silver salts unite chemically with the proteins of the tissues and discharges to form abluminates, but their action does not penetrate into the deeper tissues and is checked by sodium chloride which changes it into insoluble inert chloride.

Applied to the unbroken skin in the form of a stick or in concentrated solution, it produces at first a white stain which soon turns black from exposure to light. The stain peels off as a dark scale if the application is light, or as a black slough if the application is prolonged. It is therefore an **astringent** and **caustic.**

It is an **antiseptic** but as soon as it comes in contact with any secretion of the body or with any tissue it is precipitated as inert silver chloride. The antiseptic action is due to its forming compound with proteins of the bacteria, but since it also combines with the proteins of the tissues there is irritation which is more marked when applied to delicate mucous membrane like the conjunctiva.

The protein compounds being non-ionisable are not precipitated and therefore are less irritant and feebly disinfectant. For the same reason the colloidal compounds are not corrosives nor irritants or astringents. They have no antiseptic action even after prolonged application, the antiseptic action depending upon the ionic concentration of the different compounds.

Internally.—In the mouth and stomach silver acts as an **astringent.** It has no astringent effect in the intestine as it is precipitated as silver chloride in the stomach and reduced to metallic silver in the intestine. Moderately large doses cause gastro-enteritis with collapse and death. Silver is not absorbed in sufficient quantity to produce any general effect, but if the administration is prolonged it is

absorbed in very minute quantities, and the granules are deposited in the various parts of the body, chiefly the mouth and the gums, producing dark blue discolouration resembling lead poisoning. It causes a slate blue discolouration of the skin from deposition of the compound in all tissues of the skin except the rete Malpighii. This pigmentation or argyria is almost permanent. The same discolouration is also noticed in the conjunctiva from prolonged application of silver compounds and deposition of silver albuminate in the sub-epithelial tissue. The colouring sometimes spreads to the cornea when the vision is interfered with. This condition is known as **argyrosis** of the conjunctiva, and may be removed by the injection, after preliminary anaesthesia, of a solution of 12 p.c. sodium thiosulphate and 2 parts of a 2 p.c. solution of potassium ferrocyanide, with a fine platinum needle subconjunctivally.

Elimination.—Silver is excreted with the faeces as sulphide staining it dark brown, and by the intestinal secretion and bile. A portion is deposited in the kidneys and the liver.

Toxic action.—When given in poisonous doses the only symptoms produced are those of gastro-enteritis with vomiting and purging, extreme prostration, collapse and death. When given to animals the chief symptoms are those of central nervous system. They are paralysis of the vaso-motor centre with fall of blood pressure, disturbances of respiration and finally paralysis of the respiratory centre, general convulsion followed by paralysis beginning in the lower extremities. The heart is little affected; in fact it continues to beat even after the stoppage of respiration.

Antidotes.—In *acute poisoning* from accidental causes, mucilaginous drinks, such as thick gruel, should be immediately given to envelope the caustic ; this should be followed by an emetic or stomach syphon. Common salt is the *chemical antidote.* White of egg, milk and water, and other demulcents may be given freely.

Therapeutics of Silver Salts

Externally.—Silver nitrate may be applied to exuberant granulations, callous, indolent ulcers, fistulae, chancres, etc., because of its limited caustic and after-stimulating effects on them. It arrests bleeding from leech-bites.

Eye and nose.—A solution of silver nitrate (5 to 10 grs. in 1 oz.) is useful in granular conjunctivitis and ophthalmia neonatorum. As a preventive against ophthalmia neonatorum, both nitrate (1 to 2 p. c) and argentoprotein are largely used, the latter up to 10 p. c. solution. The conjunctiva must first be rendered anaesthetic by means of cocaine. The silver solution is then applied with a camel-hair brush, and the excess of caustic afterwards neutralised by irrigation with normal saline solution. A weaker solution (1 to 4 grs. in 1 oz.) may be used as a

collyrium in purulent conjunctivitis. A weak solution makes a valuable irrigation in rhinitis. Both protargol, and argyrol may be used in conjunctivitis as eye-drops ; the former in strengths of 2 to 20 p.c., while the latter 25 p.c. A 10 p. c. ointment of argyrol may also be used.

Genitals.—Solid caustic is still used for cauterising granular or ulcerated os and cervix. A strong solution may be injected into or painted within the womb in endometritis or endocervicitis. A weaker solution (1 to 2 grs. in 1 oz.) makes an effective injection in gonorrhoea, leucorrhoea and pruritus pudendi due to leucorrhoea. Irrigation (1 in 1000 to 10,000) has been successfully used in many cases of gonorrhoea. Injections of protargol (1 in 500 or more) or argyrol are also useful. A 2 to 5 p.c. solution may be used to cauterise chancres and indolent ulcers. Being opaque to X-rays, collargol (20 p.c. solution) is injected into the ureter and renal pelvis for diagnostic purposes.

Internally.—Unhealthy or chronic ulcers in the mouth quickly heal after being touched with mitigated caustic. A solution (10 to 20 grs. in 1 oz.) is an excellent application for sore throat, acute or chronic, pharyngitis, follicular tonsillitis, and tubercular and other ulcerations of the larynx.

As an enema (10 grs. to 1 pt.), it has been successfully employed in **chronic dysentery** and ulcerations of the bowel. Albargin 1 to 2 grains to 1 oz. makes an excellent bowel wash in cases of chronic bacillary dysentery and in colitic conditions. It should be used after a preliminary washing of the bowel with plain warm water.

Nervous system.—Silver was formerly largely used in many nervous diseases, specially epilepsy, but it is doubtful if any silver actually reaches the central nervous system, and the clinical experience has been disappointing.

Caution.—To avoid argyria, the use of the drug must be suspended as soon as a dark line is noticed on the edges of the gums which may be removed by a course of acid tartrate of potassium, or potassium iodide. But perfect restoration to the normal does not occur. Its administration must be stopped for two weeks after two months' use, however small the dose may be. The use of hexamine has given good results in some cases.

Prescribing hints.—Silver salts are given in pills after food, but if their local action on the stomach is desired they should be given on an empty stomach, preferably in solution. For application to the skin, a solution of the nitrate in nitrous ether is the best, as it does not run in drops and is a stronger preparation than the aqueous solution. The ordinary silver preparations have been largely replaced by strong and mild argentoproteins.

Silver stains on linen can be removed by washing with a solution of potassium cyanide 3 grms., iodine 0.3 grm., and water 30 mils. The stain on the skin may be removed (1) by potassium cyanide solution, but the part must be well washed afterwards ; (2) by covering the skin with solution of iodine and then washing with a

solution of sodium thiosulphate ; or (3) by washing with corrosive sublimate (10 p.c.) solution.

ZINCI SULPHAS

(Zinc. Sulph.). $ZnSO_4.7H_2O$.

Syn.—White Vitriol.—Zinc Sulphate is prepared by the interaction of zinc and sulphuric acid. Contains not less than 99.5 p.c. and not more than the equivalent of 101 p.c. of zinc sulphate.

Characters.—Colourless, transparent crystals or crystalline powder with a strong metallic styptic taste. Odourless. *Soluble* in less than 1 part of water.
Incompatibles.—Alkalies and their carbonates, lime-water, lead acetate, silver nitrate, vegetable infusions, and milk.
B. P. Dose.—10 to 30 grs. or 0.6 to 2 grms. as emetic.

Official Preparation

1. **Unguentum Zinci Oleatis.**—Contains not less than 5.2 p.c. ZnO.

Zinci Stearas. (Zinc. Stear.).—Zinc Stearate consists chiefly of zinc stearate with variable proportions of zinc palmitate. Contains not less than 13.0 p.c. and not more than 15.5 p.c. of zinc oxide.

Characters.—A light, white impalpable amorphous powder, free from grittiness ; odour, characteristic. *Insoluble* in water, in alcohol (90 p. c.), and in solvent ether.

Zinci Oxidum. (Zinc. Oxid.). ZnO. **Syn.**—Chinese White.—Zinc Oxide is obtained from metallic zinc by combustion in air. Contains not less than 99 p.c. of zinc oxide.

Characters.—A soft, white or faintly yellowish-white powder, free from grittiness ; odourless. *Insoluble* in water. *Soluble* in solutions of sodium hydroxide and dilute mineral acids.
Enters into.—Lotio Calaminae.

Official Preparations

1. **Unguentum Zinci Oxidi.** *Syn.—Zinc Ointment.*—15 p. c.
2. **Unguentum Zinci Oxidi Aquosum.**—15 p. c. with hydrous ointment.
3. **Pasta Zinci Oxidi Composita.** *Syn.—Zinc Paste ; Lassar's Paste.*—Zinc oxide 25 p.c.
4. **Gelatinum Zinci.** *Syn.—Unna's Paste.*—Zinc oxide 15 p.c.
5. **Suppositoria Hamamelidis et Zinci Oxidi.**—10 gr. zinc oxide.

Zinci Peroxidum. Syn.—Medicinal Zinc Peroxide.—A mixture of zinc peroxide, zinc oxide and zinc hydroxide. A fine white or faintly yellow powder ; odourless.

Calamina. Syn.—Prepared Calamine.—Calamine is basic zinc carbonate suitably coloured with ferric oxide.
Characters.—An amorphous, impalpable pink or pinkish-brown powder. *Insoluble* in water, soluble with effervescence in hydrochloric acid.

Official Preparation

1. **Lotio Calaminae.**—15 p.c. calamine and 5 p.c. zinc oxide.

Non-official Preparations

1. **Pasta Zinci Oxidi et Iodoformi,** B. P. C. *Syn.—ZIPP.*—Zinc oxide, iodoform, each 4 oz., liquid paraffin 5 oz.
2. **Unguentum Calaminae Co.,** B. P. C.—Calamine, zinc oxide, each 1 oz., solution of coal tar 1/2 oz., hydrous wool fat 2 oz., white soft paraffin q.s. 8 oz.

Pharmacology of Sulphate, Oxide, Peroxide and Stearate of Zinc

Externally.—The insoluble salts like the oxide, the carbonate and the stearate are mild **antiseptic** and **astringent,** and are used as local sedatives. Their action resembles lead and silver salts, *i.e.* they precipitate the proteins in the discharges and in the tissues.

Internally.—The sulphate has a metallic taste and acts as an emetic like copper but less irritating, though quite effective and prompt, and is not followed by any depression. In large doses it is a powerful **gastro-intestinal irritant** causing vomiting, purging, abdominal pain and collapse. The oxide and the carbonate are less irritant to the stomach, but their prolonged use causes dyspepsia and constipation and occasionally diarrhoea.

Zinc is eliminated by the stool, and in smaller amount by the bile and the urine. It is absorbed and stored up in the liver and to a less extent in the spleen, the kidneys, **and the thyroid.**

Little is known of its systemic effect. After prolonged use the symptoms closely resemble plumbism. In zinc mines of Silesia the workers suffer from obstinate catarrh of the respiratory tract, catarrh of the throat and constriction of the chest, a metallic taste on the mouth, gastro-intestinal irritation, general cachexia, cramps, lassitude and joint pains. Intermittent attacks of fever, known as *brass founder's ague*, sometimes occur from constant inhalation of the fumes. Some obscure nervous symptoms have been attributed to it. It depresses the central nervous system, the heart, and the muscles.

THERAPEUTICS OF SULPHATE, OXIDE, PEROXIDE AND STEARATE OF ZINC

Externally.—The sulphate (2 grs. to 1 oz. of water) forms an excellent and stimulating application for wounds and ulcers, and as an **astringent injection** in gonorrhoea, leucorrhoea, otitis, etc. It is used as an eye lotion in conjunctivitis* provided there is no ulceration of the cornea.

As a mild astringent and sedative the oxide, stearate and carbonate (calamine) are used as dusting powders mixed with talc powder or as an ointment or paste in various skin affections. As it lessens secretion, calamine is used as a drying application in eczema and intertrigo.† It is often combined with lead (*see* page 120). The suppository is useful as a sedative and astringent in **bleeding piles.**

The peroxide liberates oxygen and is used as a sedative and mild antiseptic in skin affections when it promotes healing of chronic ulcers. It inhibits the growth of *haemolytic streptococci* and all anaerobic bacteria including those causing gas-gangrene. It may be used suspended in distilled water in the form of a paste or cream (40 p.c. strength).

Internally.—The sulphate is used internally as an emetic in cases of poisoning. The oxide has been used in

*Zinc. sulph.		grs. 4
Acid. boric.		grs. 10
Aq. dest.	ad	oz. 1

†Calamin.	grs. 120
Zinc. Oxid.	grs. 120
Ol. Oliv.	oz. 1
Aq. Calcis.	oz. 1

hysteria and epilepsy, and with belladonna to check the night sweats of phthisis ; possibly it is of little value in these cases.

CUPRI SULPHAS

(Cupr. Sulph.). $CuSO_4$, $5H_2O$.

Syn.—Blue Vitriol ; Blue Stone ; *Tutia*, Beng.

Source.—Copper Sulphate is obtained by the action of sulphuric acid on copper. Contains not less than 98.5 p.c. and not more than the equivalent of 101 p.c. of copper sulphate.

Characters.—In blue triclinic prisms, or a blue crystalline powder. *Solubility.*—1 in 3 of cold water, almost insoluble in alcohol (90 p.c.).

Incompatibles.—Alkalies and their carbonates, lime water, mineral salts (except sulphates), iodides, and many vegetable astringents.

B. P. Dose.—1/4 to 2 grs. or 16 to 120 mg. ; 5 to 10 grs. or 0.3 to 0.6 grm. as an emetic.

NON-OFFICIAL PREPARATIONS

1. **Lapis Divinus.** *Syn.—Cuprum Aluminatum.*—Powdered copper sulphate, potassium nitrate and alum, of each equal parts melted in a porcelain dish, add camphor 1 and alum 1 ; 2 grs. in 1 oz. of distilled water makes a good *eye-wash*.
2. **Guttae Cuprae Sulphatis, B. P. C.**—*Syn.—Eye-drops of Copper Sulphate.*—Copper sulphate 2 gr., sod. chlor. 3½ gr., distilled water, q.s. 1 oz.

PHARMACOLOGY

Externally.—Copper sulphate has no action on the unbroken skin, but is a **caustic** when applied to a raw surface or a delicate mucous membrane, such as that of the conjunctiva. In dilute solutions it constricts local blood-vessels and it is therefore a **local astringent.** It is an **antiseptic** and in dilutions of 1 in 1,000,000 of distilled water, 1 in 50,000 of tap water, and 1 in 1,000 of sea water kills *Bact. typhosus* in two hours. The presence of organic matter still further reduces this action. It is highly poisonous to algae, fungi and protozoa. It is however not a reliable bactericide, though fairly efficacious for the bacilli of the colon group.

Internally. **Gastro-intestinal tract.**—In small doses copper has a harsh metallic taste, and acts as an astringent, and in large doses (5 to 10 grs.) as an emetic like zinc sulphate. Emesis is a reflex effect caused by its irritant action on the gastric mucous membrane. After emesis most of the copper is expelled out and no further effect is observed. If it fails to induce vomiting the stomach must be quickly emptied, otherwise gastro-enteritis may result with symptoms of acute corrosive poisoning. As a rule large single doses do not cause any harm as they are rapidly removed by vomiting.

Absorption and elimination.—Copper is absorbed with difficulty in minute quantities, either when given by the mouth or from wounds and other mucous surfaces, and is stored up in the liver, spleen and kidneys. It is eliminated almost entirely by the faeces, also by the bile, urine, saliva and sweat.

Copper in minute quantities is present in the mammalian tissue. The blood contains about 0.14 mg. per 100 c.c. and the copper content of the liver and spleen is relatively high. It is supposed to aid iron in the formation of haemoglobin in young animals (Hart and Steenbock). It has been shown that a combination of copper and iron improves induced anaemia more quickly than when iron is administered alone. It does not help absorption or storage of iron and does not enter into the formation of haemoglobin, but is said to act as a catalytic agent in its formation. It is normally present in the food, specially vegetable food and enters into a firm compound with chlorophyll.

Acute toxic action.—In large doses copper salts produce violent gastro-intestinal irritation, causing vomiting sometimes of bluish colour, metallic taste in the mouth, abdominal pain and symptoms of gastro-enteritis. Death may occur from cardiac and respiratory failure.

Antidotes.—Emetics or stomach pump if there is no free vomiting; white of egg, milk or demulcent drinks; yellow prussiate of potassium, followed by opium and a warm poultice over the stomach.

Chronic toxic action.—Workers in copper or brass may suffer from anaemia, headache, debility, emaciation, indigestion, tremors, laryngeal and pharyngeal catarrh, occasional haemoptysis, salivation, a green line at the bases of the teeth and occasional colic, in short a condition not unlike that of lead poisoning.

THERAPEUTICS

Externally.—Copper sulphate in the form of sticks is used to destroy exuberant granulation, and as a lotion (2 to 4 grs. to 1 oz.) to stimulate indolent ulcers. Being not so strong as silver nitrate, it causes less pain when applied to granular lids and to the edges of the eyelids in tinea tarsi. It is largely used in the form of *lapis divinus*.

It has also been used to sterilise water infected with typhoid bacillus but the proportion of copper is greater than required to kill algae. In strengths of 1 in 2 to 10 millions it removes algae and other vegetable growths from the water. Copper sulphate five parts per million when added to water kills water snails which act as an intermediate host of bilharziasis.

Internally.—Very rarely used internally, but has been recommended in ¼ to 1 gr. doses in actinomycosis and sporotrichosis. For its emetic action, it is occasionally used in narcotic poisoning in 1 p.c. solution. It is a valuable antidote in poisoning by phosphorus; here it acts not only as an emetic, but forms insoluble copper phosphide which is not absorbed. Three grains of copper sulphate in 2 oz. of water should be given every few minutes until vomiting is induced and then a saline laxative.

For the treatment of **anaemia** no additional copper is ordinarily required, the necessary amount is supplied by

the food. Nutritoinal anaemia of infants improve more rapidly when iron is combined with minute doses of copper.

ALUMEN

Alum. (Alum.)

Syn.—Alumen Purificatum : *Fatkiri*, Beng. *Fitkiri*, Hind.

Source.—Obtained by the combination of aluminium sulphate with potassium sulphate, and contains not less than 99.5 p.c. of potash alum ; or by the combination of aluminium sulphate with ammonium sulphate, and contains not less than 99.5 p.c. of ammonia alum.

Characters.—Colourless, transparent, crystalline masses, or a white powder ; taste, sweetish and astringent. Melts when heated and loses water of crystallisation and forms anhydrous salt. Very *soluble* in water ; insoluble in alcohol (90 p.c.) ; freely soluble in glycerin.

Gelatinum Alumini Hydroxidi, I.P.L.—Aluminium Hydroxide Gel.—Colloidal Aluminium Hydroxide is an aqueous suspension containing 3.6 to 4.4 p.c. of Al_2O_3.

Characters.—White viscous suspension, transluscent in thin layers from which small amounts of water may separate on standing.

Dose.—60 to 120 ms. or 4 to 8 mils.

Gelatum Alumini Hydroxidi Siccum, U.S.P.—Dried Aluminum Hydroxide Gel is a white colourless, tasteless, amorphous powder. Insoluble in water and in alcohol.

Dose.—Approximately 10 grs. or 0.6 grm.

NON-OFFICIAL PREPARATIONS

1. **Glycerinum Aluminis.**—13 p. c. potash alum. *Dose.*—30 to 60 ms. or 2 to 4 mils.
2. **Collutorium Aluminis, B. P. C.** *Syn.—Alum Mouth-wash.*—Glycerin of alum 1¼ oz., acid infusion of rose, q.s. 10 oz. Should be diluted with ten times its volume of warm water before use.

PHARMACOLOGY

Externally.—Alum has no action on the unbroken skin, but coagulates the albumin of discharges and tissues and forms a covering on ulcers and sores, and arrests bleeding. Hence, it is a local **astringent** and **haemostatic.** Dried alum is a mild caustic because it abstracts water.

Internally.—Alum is a local astringent to the mouth and throat, imparting an astringent taste, and a feeling of dryness to the throat. In small doses (3 to 4 grs.) it has the same astringent action on the stomach and intestine as on the raw skin, producing constipation. Its haemostatic action is entirely local. In 30 to 60 grs. doses it causes vomiting by direct action on the stomach, and in still larger doses it is a gastro-intestinal irritant causing vomiting and purging. Very little is absorbed, so that no symptoms of poisoning are elicited even after prolonged use. The small amount absorbed is stored in the liver, kidney, etc., and slowly eliminated in the bile and urine.

Elimination.—Alum is probably absorbed into the blood as an albuminate, and has no remote action on the tissues in medicinal doses. It is chiefly eliminated with the faeces and partly by the skin, bile and kidneys.

THERAPEUTICS

Externally.—In the form of powder or in a concentrated solution, it stops bleeding from leech bites, wounds and superficial cuts. A weak solution of alum and borax (1 p.c. of each) checks the discharge of weeping eczema. A solution of alum (½ p.c.) is used as a nasal wash in ozaena, and in the form of powder will check bleeding from the nose, gums and other sources. For epistaxis it may also be used as a nasal douche (10 grs. to 1 oz.). Similarly a lotion (4 to 8 grs. to 1 oz.) is useful in purulent or ordinary conjunctivitis.

Genitals.—Alum makes a good wash (60 grs. in 1 pint) for vulvitis of children, if the parts are frequently irrigated and a piece of lint soaked in the lotion is left *in situ*. It also relieves pruritus. A douche (10 grs. to 1 oz.) removes leucorrhoea, checks slight haemorrhage from patulous os after abortion or delivery. A weak solution (3 grs. in 1 oz.) is used in gonorrhoea as urethral injection.

Internally. **Alimentary canal.**—Alum is commonly used as a dentifrice in ulcerated and spongy gums. A solution (5 to 10 grs. in 1 oz.) is a useful gargle in sore throat, elongated uvula, tonsillitis, salivation, and aphthous and ulcerative stomatitis, but Glycerinum Aluminis is a better application. As an astringent, alum is used as a local haemostatic in **gastro-intestinal haemorrhage**. Alum-whey obtained by curdling 1 pint of milk with 120 grs. of alum may be given with benefit in enteric and other diarrhoeas. In 30 gr. doses frequently repeated, it is of special value in **lead poisoning** and relieves colic by precipitating lead salts as insoluble lead sulphates.

Aluminium hydroxide is used as a gastric antacid and has the advantage over other antacids in that it does not produce subsequent hyperacidity and is largely used in the treatment of **gastric** and **duodenal ulcer** and in **hyperacidity.** It forms a coating over the ulcer with a jelly-like mass and adsorbs hydrochloric acid on the solid colloid. It is also a mild demulcent and astringent, and differs from magnesium carbonate or oxide, in not being a laxative. Since it is not absorbed it does not produce alkalosis. It is non-toxic and does not influence the acid-base equilibrium. It relieves pain often within 24 hours and causes healing of niches in from 7 to 10 days, while larger craters fill up in 2 weeks. Beneficial results are obtained in patients showing no improvement with other treatment. Sufficient oil of peppermint, sugar or saccharin may be added for flavouring purpose.

KAOLINUM PONDEROSUM. (Kaolin, Pond.).—Kaolin is a native aluminium silicate, powdered and freed from gritty particles by elutriation. A soft whitish powder, insoluble in water.

Official Preparation

1. **Cataplasma Kaolini.** *Syn.—Kaolin Poultice.*—Should be kept in well-closed containers.

Kaolinum Leve. (Kalolin. Lev.).—Light Kaolin is purified native aluminium silicate free from gritty particles.

Characters.—A light, white powder; odourless and tasteless. *Insoluble* in water, and in mineral acids.
B. P. Dose.—1/2 to 2 oz. or **15 to 60 grms.**
N. B. When Kaolin is prescribed or demanded, Light Kaolin shall be dispensed or supplied. Heavy Kaolin is used in making Poultice of Kaolin.

Non-official Preparations

1. **Unguentum Kaolini, B. P. C.** *Syn.—Kaolin Mass.*—White soft paraffin 50, hard paraffin 25, melt, and add kaolin 25, stir until cold. An emollient application to abraded surfaces, and a useful excipient for silver nitrate, potassium permanganate, and bichromate pills.
2. **Emulsio Paraffini Liquidi et Kaolini, B. P. C.**—Liquid paraffin, 5 oz.; powdered acacia, 300 grs.; tragacanth powder, 40 grs.; kaolin 3¾ oz.; sod. benz. 15 grs.; chloroform water q. s. 20 oz. *Dose.*—1/2 to 2 oz. or 15 to 60 mils.
3. **Pulvis Magnesii Carbonatis Co., B. P. C.**—Heavy mag. carb., calc. carb., each 4 oz., sod. bicarb. 3 oz., light kaolin 1 oz. *Dose.*—15 to 60 grs. or 1 to 4 grms.

Action and Uses

Besides its use as an *excipient* in the preparation of pill masses, specially for substances which contain oxidising agents (potassium permanganate, silver nitrate, etc.), kaolin can be employed as a dusting powder in intertrigo, weeping eczema, etc. The cataplasma forms a valuable poultice in relieving deep-seated inflammation, and may be applied hot on a piece of thick cloth or lint in pleurisy, pneumonia, pericarditis, inflamed joints, hepatitis, etc., where it gives much relief. It should be changed every 12 to 24 hours, and kept in place with a bandage.

Internally.—Kaolin has two important actions, *viz.*—(1) forms a coating on the intestinal wall, thus protects it from irritating particles and digestive juices and reduces peristalsis, thus acting as a sedative; (2) adsorbs poisons and bacterial toxins. For its former effect it is used in diarrhoea and ulcerative colitis, while for the latter in cholera, dysentery, etc. The usual practice is to mix 100 grms. in 250 mils of water (8 ozs. to 1 pt.), 3 to 4 ozs. of this is given every half hour for the first twelve hours, and several glasses are taken during the next twelve hours. Being a very efficient adsorbent, light kaolin is used for adsorption of bacteria and toxins from the intestine thus preventing their absorption. *Kaolin has no direct disinfecting action on the intestine.* It is used in gastritis, gastric and duodenal ulcer and hyperacidity, and is generally combined with bicarbonate of soda and carbonate or oxide of magnesium.* It is also combined with liquid paraffin.

* Sod. Bicarb.	oz. 1½
Mag. Oxid. Pond.	oz. 1
Bism. Carb.	oz. 1/2
Calc. Carb.	oz. 1½
Kaolin. Lev.	oz. 1½
Pulv. Zingib.	grs. 120

1/2 to 1 teaspoonful for a dose.

* Mag. Carb. Pond.	oz. 1
Sod. Bicarb.	oz. 1/2
Kaolin. Lev.	oz 3/4
Ol. Menth. pip.	ms. 10

1/2 teaspoonful for a dose.

Depilatory

THALLIUM

THALLII ACETAS. (Not official).—Prepared by neutralising an aqueous solution of thallium hydroxide with acetic acid. In colourless needles, or in white crystalline powder, soluble in water.

Dose.—8 mg. (1/8 gr.) per kilogram of body weight.

Action and Uses

Thallium salts produce no immediate effects on animals beyond causing some relaxation of the plain muscles, but a few days later (generally a fortnight) cause shedding of the hair in all animals. Its chief use is as a **depilatory** in cases of ringworm of the scalp, when the hair becomes brittle in a week's time and falls off within the next week, and the hair starts to grow in about the same time. It is generally administered in tablets or sweetened aqueous solution, and since children tolerate it better its use is confined to children under ten years of age. As a rule one dose is sufficient and the drug is not repeated within a period of three months.

Since the drug is apt to produce toxic symptoms it should be used with extreme caution, and the dose should be well regulated. Large doses will cause shedding of hair from all parts of the body innervated by the sympathetic. Toxic symptoms are vomiting, diarrhoea, stomatitis, albuminuria, joint pains confined to lower limbs, peripheral neuritis, delirium and collapse. Remember that the *margin of safety* between the epilation dose and the toxic dose is very low, and it should not be used when there is albuminuria or **any general constitutional disease.**

Treatment of poisoning.—Stomach wash or an emetic followed by a purgative. In acute cases dextrose intravenously. Caffeine or adrenaline to overcome shock, and sodium iodide (5 to 15 grs. daily) to convert the toxic soluble thallium salts into almost insoluble iodides. Sodium thiosulphate (5 to 15 grs. daily) intravenously to promote gradual elimination. Children should receive proportionately smaller doses.

GROUP IV

METALLOIDS

Bismuth, Arsenic, Antimony, Chromium, Phosphorus

Bismuth, Arsenic and Antimony will be discussed with other Chemotherapeutic Agents.

CHROMII TRIOXIDUM. (Chrom. Triox.). Syn.—Acidum Chromicum; Chromic Anhydride.—Chromium Trioxide is obtained by the interaction of sulphuric acid and potassium dichromate. Contains **not less than 95 p.c. CrO_3.**

Characters.—Dark-red, acicular crystals, or dark-brown masses. No odour, deliquescent and corrosive. *Freely soluble* in water and in solvent ether.

N. B.—Liable to cause combustion, or **explosion when in contact with alcohol, ether, glycerin and other organic substances.**

Pharmacology and Therapeutics

Externally.—It is a powerful oxidising agent, destroying the lower organisms, and is therefore a **deodorant** and **disinfectant.** It is powerfully hygroscopic and takes up water from moist tissues and oxidises organic substances, and acts as a **caustic.** Liquor acidi chromici (25 p.c. solution) is used for destroying **warts.** It should be applied with a pointed glass rod, the adjacent parts being protected by a plaster or ointment, and a piece of wet lint kept ready to absorb any superfluous acid. A weak lotion (1 in 40 or more) is useful for **ulcerated gums** and **foul sores. A 3 per cent. solution** checks perspiration of the feet.

PHOSPHORUS. (Not official).—A semi-transparent wax-like solid, emitting white vapours and is luminous in the dark ; ignites in the air. *Solubility.*—Insoluble in water ; soluble 1 in 25 of chloroform, 1 in 350 of alcohol (90 p. c.), 1 in 80 of olive oil and of ether ; 2 in 1 of carbon disulphide, 1 in 60 of oil of turpentine.

Dose.—1/100 to 1/25 gr. or 0.6 to 2.5 mg.

NON-OFFICIAL PREPARATIONS

1. **Calcii Hypophosphis, B. P. C.**—A white, crystalline pearly salt. Taste, bitter, nauseous. Almost completely soluble in water. *Dose.*—3 to 10 grs. or 0.2 to 0.6 grm.
2. **Syrupus Calcii Hypophosphitis.**—Contains 1 gr. per 1 dr. *Dose.*—1 to 4 drs. or 4 to 16 mils.
3. **Calcii Glycerophosphas, B. P. C.**—A calcium salt of glycerophosphoric acid. A fine, white, hygroscopic odourless powder. *Dose.*—3 to 10 grs. or 0.2 to 0.6 grm.
4. **Ferri Glycerophosphas, B. P. C.**—*Dose.*—1 to 5 grs. or 0.06 to 0.3 grm.
5. **Sodii Glycerophosphas, B.P.C.**—*Dose.*—5 to 10 grs. or 0.3 to 0.6 grm.

PHARMACOLOGY

Phosphorus is an important constituent of the body and forms about 0.7 p. c. of the body weight. It exists in bone as phosphate of calcium and magnesium, and as soluble phosphate ions in the blood and other fluids, and as nuclein, lecithin and phosphatides in the tissues and plasma. It has a specially intersting physiological action. As a poison it is important.

Stomach and liver.—Moderate doses produce, after a delay of some hours or even days, nausea, vomiting, abdominal pains, rarely diarrhoea and jaundice ; the vomited matter is luminous in the dark, and has a garlic odour. Liver becomes enlarged, painful and tender and undergoes fatty changes.

Blood.—Phosphorus is absorbed in the small intestine and circulates as such. In therapeutic doses it increases the number of red blood corpuscles and retards coagulation of the blood due to destruction of fibrinogen or fibrin ferment, or to the formation of peptone bodies from protein destruction. This factor and the fatty degeneration of the endothelial tissue of the capillaries account for haemorrhage in poisoning.

Bones.—When continued long in such minute doses as not to affect the stomach or liver, it has a specific action on the bone. There is an increased osseous deposit and the long bones become more dense at the expense of the cancellous tissue. Instead of the porous bone tissue filled with red marrow there develops from the epiphysis line a dense, hard substance of the same nature as that forms on the outer shell on the diaphysis. The bone-marrow in chronic poisoning becomes hyperaemic, the fat cells disappear and the leucoblastic cells increase.

Metabolism.—In small doses continued long phosphorus stimulates metabolic processes and helps growth and formation of new tissue. The destructive effects are observed in chronic poisoning, or as a secondary process after a single large dose. The main symptoms are characterised by increased tissue destructions with disturbances of synthesis, oxidation and dissociation. Less fat but more carbohydrate and protein are broken up, though imperfectly, and the excretion of nitrogenous metabolites, *viz.*, amino acids, leucin, tyrosin and peptone like bodies is increased. The excretion of urea is not increased, on the contrary may be diminished, but there is an excess of ammonia which enters the blood to neutralise acidosis formed by the production of lactic acid and other organic acids as a result of incomplete oxidation of fat, glycogen, etc. The respiratory interchange is diminished and oxygen consumption and carbonic acid excretion is reduced. The cause of this diminished oxygen intake is not definitely settled, although it has been suggested that phosphorus renders the cells less capable of utilising oxygen.

Fatty infiltration occurs in almost all organs of the body, that of the liver being most extensive. Another important effect is the change in the carbohydrate metabolism with disappearance of glyco-

gen from the liver. The increased excretion of nitrogen has been regarded as the result of this effect since the body draws on the protein to make up the deficiency of the carbohydrate. Moreover, the emptiness of glycogen of the liver leads to mobilization of the fats to supply the want, and since the liver cannot utilise the fat completely it is deposited in the cells of this organ.

Chronic toxic action.—Chronic poisoning is rare, *and occurs only in those workmen who are exposed to the fumes* of phosphorus. Gastro-enteritis, fatty degeneration, necrosis of the jaw, predisposition to general tuberculosis are the prominent symptoms. Phosphorus fumes attack the bone through carious teeth or spongy gums, but this effect is not produced by its internal use.

THERAPEUTICS

As a nervine tonic the hypophosphites and the glycerophosphates have been used in nervous **exhaustion, over-taxation of the brain** from prolonged strain and overwork, but as they pass unchanged through the system and can be almost entirely recovered from the urine, they can furnish no phosphorus to the nerve tissue. They are used largely in wasting diseases like **phthisis,** and in **chronic bronchitis,** but with doubtful results. It has been used in **rickets,** in **ununited fractures** specially during pregnancy, and in **osteomalacia** but its use in these conditions has been given up in favour of cod-liver oil, vitamin D, ultra-violet rays, and sunlight.

Recently **radioactive phosphorus** in the form of phosphate has been used in certain blood dyscrasias, chiefly **leukaemia** and **primary polycythaemia.** It is a product of cyclotron by which red phosphorus of atomic weight 31 (P_{31}) captures a neutron and acquires an atomic weight of 32. This is radioactive phosphorus (P_{32}). It emits *beta* rays only.

The dose is measured in millicuries ; one mc. is that amount of radioactive substance of which 37 million atoms disintegrate per second. It may be administered either orally or intravenously. Given orally 15 to 50 p.c. is excreted in the urine during the first six days. As a rule 25 p.c. is lost in the faeces and 75 p.c. is absorbed. The excretion is less in leukaemic and polycythaemic patients.

Preparation generally used is an isotonic solution of dibasic sodium phosphate containing 15 mg. per c. c. With the addition of isotonic saline the specific activity of 1 c.c. is 1 mc. This is given intravenously as then a more accurate relationship can be maintained between the amount retained and the dose administered than when given orally.

The treatment is yet in its experimental stage and it is possible that it may prove a useful adjunct to X-ray treatment.

GROUP V

DRUGS ACTING ON THE NERVOUS SYSTEM

By the nervous system we mean the brain, the bulb, the cord, the nerves, both sensory and motor, and the various ganglia. The highest motor and sensory centres as well as those of volition, intellect, emotion, etc., are contained in the cerebral convolutions, while the simple automatic and reflex centres are in the basal ganglia, cerebellum, medulla and cord. All nerve centres are connected with one another by nerve filaments called *collaterals*, for co-ordination of impulses. The cerebral or highest centres are not only excitable or capable of being brought into action by afferent impulses, but also possess an inherent power of spontaneously originating impulses themselves.

Their action is therefore both *Reflective* and *spontaneous*. To the pharmacologist this reflective or *reflex action* is important. It is effected by (1) an afferent sensory nerve ; (2) reflex centre ; and (3) an efferent motor or secretory nerve. An impression excited by an irritant on the skin or other structures of the body is conducted through an afferent nerve *via* the posterior root ganglion, to the spinal cord, where it produces certain protoplasmic disturbance, resulting in a force, which either remains there as potential energy, or is conveyed by a different tract—efferent nerve—to perform some specific action either in the muscle, viscera, or the blood vessels. This process is spoken of as reflex action. This sensory stimulus instead of being reflected from the cord may be conveyed by the sensory tracts to the sensory area of the brain, where it will be perceived as an impression either of pain, heat or cold, and so forth, to be felt at the seat of stimulus, and then lead to volitional conveyance of impulse in the form of movement, etc. It will be observed that although the stimulus originates in the skin or other structures, it is perceived as a sensation in the brain. Thus an impression which is peripheral in origin becomes a sensation which is cerebral.

In considering the action of drugs on the nervous system we find that some affect one centre, while others another ; a few influence the lower centres only ; others, centres for emotion and intelligence ; and lastly some alter the nervous mechanism of different viscera.

Drugs acting on the nervous system may be classified as follows :—

Class A : Drugs acting on the cerebrum

1. Intoxicant ; **Alcohol**
2. General anaesthetics and narcotics : **Chloroform, Ether, Ethyl Chloride, Trichloroethylene, Vinyl Ether, Ethylene, Nitrous Oxide, Cyclopropane**
2. Hypnotics and narcotics : **Opium, Pethidine, Cannabis Indica, Chloral Hydrate, Chlorbutol, Butyl-chloral Hydras, Paraldehyde, Tribromoethyl Alcohol, Amylene Hydrate, Bromethol** (Avertin), **Sulphonal, Barbitone, Soluble Barbitone, Carbromalum, Phenobarbitone, Soluble Phenobarbitone, Hexobarbitone, Soluble Hexobarbitone, Phemitone, Soluble Pentobarbitone** (Nembutal), **Soluble Phenytoin** (Dilantin), **Soluble Thiopentone,** (Pentothal Sodium), **Amytal, Sodium Amytal, Urethane, Bromides, Hyoscine Hydrobromide.**

Class B : Drugs acting on the medulla

1. Medullary stimulants : **Leptazol, Nikethamide, Picrotoxin, Camphor**

Class C : Drugs acting on the cord

1. Convulsant : **Strychnine**
2. Anticonvulsants : **Chloral Hydrate, Bromides, Phenobarbitone, Methylphenobarbitone** (Prominal), **Phenytoin Sodium** (Dilantin), **Tridione, Mesantoin, Myanesin**

Class D : Drugs acting on the autonomic nervous system

1. Drugs stimulating the parasympathetic endings : **Pilocarpine, Physostigmine, Neostigmine, Muscarine, Acetylcholine, Carbachol**
2. Drugs depressing the parasympathetic endings : **Belladonna, Hyoscyamus, Stramonium**
3. Drugs stimulating the sympathetic endings ; **Adrenaline, Ephedrine, Amphetamine** (Benzedrine), **Ergotoxine** (small doses), **Tyramine**
4. Drugs depressing the sympathetic endings ; **Ergotoxine** (large doses), **Apocodeine**

Class E : Drugs acting on the motor nerve-endings and the ganglia
Curare, Nicotine, Gelsemium, Conium, Lobeline

Class F : Drugs depressing the sensory nerve-endings
Cocaine, Benzocaine, Orthocaine, Butacaine Sulphate, Butyl Aminobenzoate, Procaine Hydrochloride, Amethocaine Hydrochloride (Decicaine), Cinchocaine Hydrochloride (Nupercaine)

Class G : Drugs stimulating the sensory nerve-endings
See Counter-irritants

Class A : Drugs acting on the Cerebrum

The structure of the brain, being complicated, our knowledge of the pharmacology of this organ is obscure. Although we can influence the functions of the brain more rapidly, yet we cannot localise the action of drugs, nor can we explain the exact manner by which they produce the different symptoms. It has, however, been found that they follow certain laws while acting on the brain :

(*a*) *The law of dissolution.*—This consists of the progressive action of a drug on the nerve centres in the reverse order of their development in animal life, *i.e.* those that are the highest, and developed last are affected first, and then the next to the highest, and so on, until the lowest ones are affected. Thus alcohol paralyses the highest centres as those of will, intellect, etc., then those of the muscles, as is evidenced by staggering gait, and lastly those of the heart and respiration.

(*b*) *The law of primary stimulation and subsequent depression.*—This is well illustrated by the action of a drug which in small doses stimulates certain functions, and in large doses depresses them, *e.g.* chloroform.

The different nerve cells react differently to drugs. Thus the functional activity of the brain is influenced by a special group of drugs ; of these some like caffeine, atropine, camphor, cocaine, etc., excite the brain and are called **cerebral stimulants.** In certain instances the excitement is of a disorderly nature accompanied by incoherence and delirium, and the drugs so acting are known as *deliriants*, *e.g.* atropine ; while others produce mirthful and comfortable feelings, when they are called *exhilarants, e.g.* camphor, cannabis indica. Another group of drugs depress the activity of the brain and these are known under different names according to the nature of their action, viz.—**hypnotics, narcotics, general anaesthetics.** Alcohol, ether and chloroform produce a certain amount of excitement at the beginning, and subsequently according to the quantity used, alcohol produces *intoxication and narcosis*, chloroform and ether produce *loss of consciousness with general anaesthesia* ; and opium, cannabis indica, chloral hydrate, etc., act as *hypnotics or narcotics.* Some of these again, specially opium, act as an **analgesic** from central effect.

Others again show a selective action on certain parts

of the central nervous system. For instance, morphine while stimulating the cardiac vagus centre depresses the respiratory centre ; apomorphine acts chiefly on the vomiting centre ; amphetamine, caffeine and cocaine stimulate the psychic centre ; atropine and camphor the motor centre ; and quite a large number of drugs act on the vital medullary centres. Another group of drugs produce very little effect on the brain but influence the activities of the spinal cord or the different nerve-endings.

The brain is highly sensitive to oxygen supply and its deficiency affects it more quickly than any other tissue of the body. Thus oxygen lack causes unconsciousness, e.g. inhalation of pure nitrogen, carbon monoxide gas, etc.

I. Intoxicant

ALCOHOL

Alcohol (95 p.c.). (Alcoh.)

Source.—Alcohol (95 p. c.) is a mixture of ethyl alcohol and water, obtained by the distillation of fermented saccharine liquids. Contains 95.2 p. c. v/v or 92.7 p. c. w/w, and not less than 94.7 p. c. v/v or 92.0 p. c. w/w of C_2H_6O.

Characters.—A colourless, transparent, mobile and volatile liquid, with characteristic spirituous odour. Taste, burning. Burns with a blue smokeless flame.

Spiritus Methylatus Industrialis.—(Sp. Meth. Indust.).—Industrial Methylated Spirit is a mixture made by a legally authorised methylator, of 19 volumes alcohol (95 p. c.), with 1 volume of approved wood naphtha, and is of the quality known as '66 O.P. Industrial Methylated Spirits.'

Characters.—Similar to those of alcohol (95 p. c.), but having in addition the odour of wood naphtha.

Official Diluted Alcohols

1. **Alcohol** (90 p. c.). *Syn.—Rectified Spirit.*—Dilute 947 mils of alcohol (95 p.c.) to one litre with distilled water.
2. **Alcohol** (80 p.c.).—Dilute 842 mils of alcohol (95 p.c.) to one litre with distilled water.
3. **Alcohol** (70 p.c.).—Dilute 737 mils of alcohol (95 p.c.) to one litre with distilled water.
4. **Alcohol** (60 p.c.).—Dilute 632 mils of alcohol (95 p.c.) to one litre with distilled water.
5. **Alcohol** (50 p.c.).—Dilute 526 mils of alcohol (95 p.c.) to one litre with distilled water.
6. **Alcohol** (45 p.c.).—Dilute 474 mils of alcohol (95 p.c.) to one litre with distilled water.
7. **Alcohol** (25 p.c.).—Dilute 263 mils of alcohol (95 p.c.) to one litre with distilled water.
8. **Alcohol** (20 p.c.).—Dilute 210 mils of alcohol (95 p.c.) to one litre with distilled water.

Note.—On mixing alcohol and water contraction of volume and rise of temperature occur.

The following is the list of wines, showing the amount of absolute alcohol by weight :—

Spiritus Frumenti (Whisky) 40 p.c. v/v of alcohol ; Rum, Gin, and strong Liqueurs, about 51 to 59 p.c. ; Hocks, Burgundy, about 9 to 13 p.c. ; Spiritus Vini Gallici (Brandy) 40 to 50 p.c. ; Sherry, Port, Madeira, about 18 to 22 p.c. ; Champagne, about 10 to 13 p.c. ; Claret, 8 to 12 p.c. ; Cider, 6 to 13 p.c. ; Ale and Porter, about 3 to 7 p.c. ; Beer, 2.5 to 3.5 p.c. ; Koumiss and Ginger Beer, about 1 to 3 p.c.

PHARMACOLOGY

Externally.—Alcohol has a great affinity for water, it coagulates **protein** and irritates and destroys cells. It is therefore a **protoplasmic poison** and **astringent.** It is an **antiseptic**, and it has been found that in the preparation of alcoholic liquors the activity of yeast is retarded when the strength of alcohol reaches 10 p.c. and completely stopped when it reaches 15 p.c. When applied to the skin it evaporates quickly producing a sensation of cold which is more marked when used diluted with water. On the other hand if the evaporation is checked, or if it is rubbed in, it abstracts water from the skin and renders the skin drier and harder ; owing to this property it diminishes the secretion of sweat and is an anhydrotic. When applied in sufficient concentration (60 to 80 p.c.) it dilates the local blood vessels, produces a feeling of warmth, and renders the skin red, thus acting as a local **rubefacient** and **counter-irritant.**

Internally.—Undiluted alcohol has the same action on the mouth as on the skin, *viz.*, it coagulates the protein and abstracts water and acts as a local irritant. It stimulates the nerves of taste and causes a reflex flow of saliva, and excites the psychic secretion of gastric juice.

Stomach and intestine.—The action of alcohol on the stomach may be considered from three points of view : (*a*) its chemical effect on the stomach contents, (*b*) its effects on the stomach functions, and (*c*) its effects on the coats of the stomach. While undiluted whisky or brandy will precipitate proteins of food and possibly pepsin, and also interfere with the process of digestion, moderate quantities of diluted alcohol (below 20 p.c.) have only a negligible action on the chemical process of digestion. Wines and malt liquors, owing to the presence of organic acid and colloidal constitutents, if taken in large quantities, have a deletérious effect on digestion. In the same way red wines, owing to the presence of tannin, retard digestive process by precipitating proteins more than white wines.

In weak solutions, *i.e.* below the strength of 10 p.c., alcohol has practically no effect on the stomach wall beyond dilating the vessels and causing a feeling of warmth, but in large and repeated doses, or in concentrated solutions, it irritates the mucous membrane, increases the secretion of mucus, and retards the secretion of gastric juice. If this process is continued over long periods, as in chronic alcoholics, gastric follicles atrophy and dyspepsia becomes permanent.

In moderate strengths and taken with food or after food, it tends to promote digestion by direct stimulation of the fundus of the stomach, causing an abundant secretion of gastric juice. If taken with bitters before food it

increases the appetite juice, although a small quantity will often produce manifestations of intoxication. Apart from this effect alcohol appears to have a specific action on the secretion after absorption. Thus when alcohol is given per rectum or injected directly into the blood the same result is obtained though less in quantity.

While some observers noticed increased movements in strengths up to 20 p.c., others showed retarded motility. Clinically, alcohol seems to increase motor functions and solutions of alcohol act as carminative.

A moderate dose of strong alcohol, *e.g.* whisky or brandy, on reaching the stomach, at once **reflexly stimulates** the heart, raises the blood pressure, quickens the pulse and increases the respiratory movements. Since it causes dilatation of the vessels, specially of the skin, and increases the functional activity of different organs, alcohol is regarded as a general stimulant. But, as will be seen later, these effects are not dependent upon a direct stimulation of the nerve centres, but are purely reflex phenomena. Irritation of the mucous membrane, emotional excitement and increased movement are responsible for the acceleration of the heart.

Alcohol is so much diluted by the time it passes the pylorus that it exerts very little effect in the intestine. After an excessive amount some reaches the duodenum and acts as an irritant. Owing to increased formation of secretin pancreatic secretion is very largely increased whether alcohol is given by the mouth or per rectum. Brandy has a reputation among the lay public as an astringent in diarrhoea.

Liver.—After absorption alcohol passes directly to the liver through the portal circulation, where it affects the hepatic cells producing inflammation. It may disappear in a few days if no more alcohol is taken, but if long continued, it produces permanent changes in the liver leading to cirrhosis or fatty **degeneration**, or both. Moderate amounts as a rule are sufficiently diluted by the portal blood, but excessive drinking surcharges the portal blood with alcohol.

Food value of alcohol.—The question whether alcohol is a food has been much discussed, and the chief point is whether it can be regarded as a protein sparer. Proteins contribute to the formation and repair of tissues; carbohydrates and fats are sources of heat and energy. Since alcohol does not contain any nitrogen, it cannot replace protein and therefore has no power to build tissues. Whereas about 90 p.c. of alcohol taken disappears in the body and is converted into CO_2 and water, alcohol by virtue of the chemical energy thus liberated can replace carbohydrates and fats in the diet, and in this sense it is a **non-nitrogenous**

food. But when taken with other foods it economises the use of fat and carbohydrate, which in their turn are stored in the body, the carbohydrate as glycogen, and fat in the tissues. As alcohol does not require digestion it is in a sense superior to other foods. Moreover, it does not require more energy for absorption than other foods.

Although it cannot replace protein, alcohol will, under certain conditions, spare the protein in the same way as fat. It has been experimentally shown (Rosemann and Neumann) that on an ordinary diet the nitrogen equilibrium is maintained at a constant level, but if part of fat is withheld from the same diet, nitrogen excretion increases, showing destruction of protein, *i. e.* proteins are being drawn upon to supply the energy required in place of fat. If, however, an amount of alcohol chemically equivalent to the omitted fat is added to the diet, nitrogen equilibrium again becomes established. It is thus evident that alcohol is able to spare protein in the same way as the fat, and can thus prevent tissue waste. Alcohol therefore may be regarded as a food in the sense that it will, when given with other foods, replace carbohydrate and fat for a short time and would supply energy and spare protein and prevent tissue waste. But the value of alcohol as a food is limited because the supply of energy is fixed and cannot be adjusted according to the needs of the body, nor can it be increased to meet sudden emergency, because it cannot be stored in the body like fat or carbohydrate as reserve.

Nervous system.—In moderate doses, the action of alcohol on the nervous system is that of **apparent stimulation** which is followed, according to the quantity used, by that of **sleep** and **coma**. In small doses (about 1 oz.), it produces a feeling of mental and physical well-being. This is the *first stage* of intoxication. Imagination becomes brighter, feelings elevated, intellect clearer (highest functions of the brain), senses more acute, bodily activity more predominant, and some of the lower appetites sharpened. Since the critical faculty is dulled the subject feels extra confident, and this in itself may increase his efficiency in simple tests ; his writing will be more brisk but less accurate. If the dose is increased, the *second stage* of intoxication is observed. While a novice loses self control, a confirmed drinker is able to hide it and pulls himself together. Eventually however the judgment fails while the imagination, emotion, and power of speech are still excited, then the imagination and will power give way. If indulgence is continued further, symptoms of acute alcohol poisoning appear so that the mental balance is lost. The subject talks, laughs, sings or cries without restraint, but gradually he loses control over these functions also,

thus the speech becomes thick, incoherent and at last suspended. The muscles next get affected, at first the delicate movements, such as writing, playing on the piano, etc., are abolished. But if the dose is very large there is complete insensibility, narcosis, muscular relaxation with involuntary passage of urine and stool and subnormal temperature. The breathing becomes stertorous with cyanosis, finally the patient dies from respiratory paralysis. It will be seen that in its progressive action either of stimulation or of depression it follows the law of dissolution (*see* page 135). But the explanation of these effects is not very clear. Binz and his followers maintain that alcohol first stimulates the nerve cells in the central nervous system and subsequently depresses them, and we have already noticed that in small doses it stimulates the higher functions of the brain which functions are subsequently depressed by larger doses. The other view is that of Schmiedeberg. He holds that alcohol acts as a narcotic from the very commencement and the symptoms of stimulation are the effect of the depressant action on certain higher cerebral functions which normally exert a controlling influence, *viz.,* the will and self-restraint. This latter view seems to have more supporters and is generally accepted.

Observations have shown that when alcohol is taken without any exhilarating company, many of the manifestations are not elicited. In fact the effects depend upon the nature of the environment and on the inherent mentality of the individual, and would produce quite diverse symptoms on different persons and different effects on the same individual under different conditions. Owing to a certain degree of freedom from restraint, the person will be talkative, boisterous, sentimental or melancholic according to his individual peculiarities.

The anaesthetic actions of alcohol is well described in the book of Proverbs of Solomon. In fact this is the first description given. *

Circulation.—The reflex effect of alcohol in stimulating the circulation and respiration has already been mentioned. But its action after absorption is uncertain and depends on several factors, viz., the dose and concentration, the mode of administration and the condition of the individual. After absorption there is increased blood flow

*A man says, "They beat me, and I felt it not ; I will seek it yet again." He got beaten, but he got drunk first, and he did not feel the blows. It is, however, more for the anaesthetic action on the mind that alcohol is generally taken. Again in the book of Proverbs one gets the description of this action ; "Give strong drink unto him that is ready to perish, and wine unto those that be of heavy hearts. Let him drink and forget his poverty, and remember his misery no more."

through the skin from dilatation of the skin vessels giving rise to a feeling of warmth but those of the internal organs specially of the splanchnic area, constrict so that it allows more blood to pass through the vital organs, chiefly the heart and the central nervous system, and causes a **rise of blood pressure.** The normal heart muscle is not affected in small doses, but when exhausted it may be stimulated. During the stage of intoxication the pulse is accelerated due to excitement. The output of the heart, the force and amplitude of the pulse, and the circulation in general are more or less improved. When large doses are taken, the stimulant effect is followed by depression with fall of pressure due to dilatation of the splanchnic vessels replacing the constriction of the first stage. It should be noted that the heart which is stimulated at first is more exhausted than before after the temporary effect has passed off. Large doses do not stimulate the heart at all, in fact the heart is paralysed both reflexly and after absorption.

Respiration.—We have already observed that the medullary centres are affected last, in fact, respiration, though it becomes stertorous, does not stop even after the patient has become completely unconscious and all the reflexes are abolished. The respiratory centre is stimulated reflexly from the stomach before absorption however, but whether the centre is stimulated after absorption has been the subject of careful observation, and it is generally agreed that although the centre is not stimulated to any marked degree in small doses it is not depressed except after large doses and that even as a late symptom of poisoning. In fevers and diseases of the lungs like pneumonia, the respiration is slowed and steadied not from any direct action on the centre but through its narcotic effect it lessens excitability and anxiety and appreciation of distress.

Muscular system.—It was formerly believed that alcohol increases the physical power for more work, but later observations have shown that it is not so, although in the beginning the muscular strength increases through increased circulation in the nervous system. This is soon followed by diminution of working power, so that the total amount of work done is less.

Alcohol is taken after severe muscular work not for any stimulant effect, but for its depressing effect on the nervous system which gives a feeling of comfort and well-being while forgetting fatigue. In fact observations made with ergograph have shown that muscular work is not increased but it lessens the appreciation of fatigue so that the workers think that they have done more work, or perhaps may do more work, not from increased capacity but from lessened appreciation of tiredness.

Skin and kidneys.—Alcohol is a mild **diaphoretic** due partly to the dilatation of the skin vessels and partly to its effect on the sweat glands. But the diaphoresis depends on the renal excretion and in cold climates instead of diaphoresis there is **diuresis,** and the large quantity of water taken with alcohol is excreted by the kidneys. There is also some dilatation of the renal vessels. If alcohol is taken in large amounts a portion is excreted in the urine unchanged. Gin has a greater diuretic effect than other spirits. Prolonged use produces changes in the renal cells and may give rise to chronic nephritis.

Temperature.—Alcohol acts as a mild **antipyretic** by increasing the heat loss (*a*) from dilatation of the cutaneous blood vessels thereby producing increased perspiration and radiation, although it causes a subjective feeling of warmth ; and in larger doses (*b*) by acting on the heat regulating centre which is rendered less sensitive. It should however be noted that after very large quantities of alcohol the dilatation of the cutaneous vessels may proceed to such an extent that death may follow from excessive radiation of heat, though the drinker may feel a sense of temporary warmth in the beginning, if his vessels were contracted previously from cold air. It is therefore harmful to take alcohol during exposure to cold, for although there is a subjective sensation of warmth it lessens the power of the body to conserve heat.

Tolerance.—Long continued use produces tolerance so that a patient can take quite a large dose without showing any of the symptoms of intoxication. To these persons it is necessary to use large doses to produce the desired effect. Two factors are concerned in the production of tolerance, viz., capacity of the tissue to oxidise alcohol as soon as it is absorbed, and that the brain reacts less than normally. It is for this reason that symptoms of intoxication do not appear when a large quantity of alcohol is taken by a habitual drinker.

Absorption and Clearance.—Taken by the mouth about 20 p.c. is absorbed by the stomach, the rest is passed into the intestine to be completely absorbed and no alcohol reaches the colon. It is broken down almost entirely in the body, only from 2 to 10 p.c. which escapes combustion is excreted by the breath, skin and urine unchanged. It appears in the blood within five minutes after administration by the mouth, and it reaches highest concentration within an hour and a half. Many factors influence absorption, the food factor being important. Its distribution in the different tissues is fairly uniform, but its concentration in the brain and spinal cord is slower in rising as also in falling than in other tissues. About 5 to 15 mils are burnt in

an hour by man. This oxidation takes place chiefly in the liver and that insulin is necessary for this function.

It is generally believed that a concentration of 0.01 p.c. in the blood produces no effect ; 0.015 p.c. may cause incoordination leading to motor accident ; 0.2 to 0.4 p.c. in the blood or urine implies moderate intoxication ; over 0.4 p.c. marked intoxication in most ; and over 0.5 p.c. in all. The concentration of alcohol in the blood of living animals in deep narcosis is 0.7 p. c. A percentage of 0.8 or over means death. The concentration of alcohol in the urine is 30 p.c. higher than in the blood.

Acute toxic action.—When an excessively large dose is taken the stage of stimulation is soon followed by that of narcosis with impairment of sensation and motion, etc., already described under nervous system. Death is relatively rare, but may occur suddenly from reflex stoppage of the heart, or the coma may become deeper and death may occur from paralysis of respiration or the heart, or from pulmonary oedema, generally within twenty-four hours, if coma continues for more than twelve hours recovery is exceptional.

Treatment.—Evacuate the stomach by pump or emetics, such as apomorphine. If the patient cannot swallow, coffee with ammonia may be introduced with the pump after stomach washing. Inhalation of CO_2 with oxygen for respiration and cyanosis ; strychnine subcutaneously, or caffeine. Subsequent headache and nervousness require bromides, feeling of depression and gastritis should be treated with bicarbonate of soda, and sal volatile.

Chronic toxic action or "Alcoholism" is induced by prolonged alcoholic indulgence. Insomnia, muscular tremor, and gastric disturbance are the early symptoms. Gastritis, peripheral or multiple neuritis, cirrhosis of the liver causing ascites, chronic interstitial nephritis causing anasarca, dilatation of the heart, gout, nervous disorders, such as delirium tremens, epilepsy, paralysis, insanity, etc., are the diseases which afflict confirmed drunkards. Chronic alcoholics exhibit a train of symptoms which are grouped under the heading of *Korsakow's psychosis*, in which emotional tendencies, untruthfulness, indiscretion, mental confusion with loss of memory for recent events, and loss of idea of space and time are often present. Generally they are thin, but a few, especially those who drink beer, get fat. They cannot withstand well any serious illness, such as pneumonia, and are particularly liable to attacks of phthisis. Gin drinkers mostly suffer from cirrhosis of the kidney and liver.

Treatment of Chronic Alcoholism.—Till lately all attempt to treat this condition, that is, to make the patient abstain from taking alcohol was unsuccessful. The introduction of **Tetraethylthiuram Disulphide** (*Antabuse*) has altered the situation to some extent. Though not a direct cure, it is a valuable aid to other methods of treatment like psychological and environmental rehabilitation. It acts by producing intolerance to alcohol. The addict becomes sensitised so that subsequent ingestion of alcohol produces unpleasant symptoms of the nature of vaso-motor disturbance. Antabuse interferes with the normal metabolism of alcohol in the body and produces a high concentration of acetaldehyde which is responsible for the unpleasant symptoms.

It is given in doses of 0.25 to 0.75 grm. (4 to 12 grs.) *daily*. The dose varies in different individuals and requires to be adjusted. The treatment is best carried out in a hospital or institution.

Therapeutics

Extenally.—A weak alcoholic solution, e.g. eu-de-cologne, is useful as a cooling application in febrile headache, acute inflammation, sprains, etc. A 40 to 50 p.c. solution when rubbed hardens the skin and prevents bed sores, similarly when rubbed into the body checks excessive perspiration and brings back warmth to the surface in collapse. Since phenol has greater affinity for alcohol, it is used in injury to the skin (phenol burns) but should be washed off immediately. Liniments containing alcohol are used as counter-irritants in stiff joints, chronic rheumatism, bronchitis, pneumonia, etc. Absolute alcohol is sometimes injected into nerves in neuralgias, when it relieves the pain by causing degeneration of the particular nerve, and the pain does not recur till the nerve has regenerated again, which takes several months.

Alcohol (70 p.c.) is used for washing the skin and the hands before operation, for sterilising delicate instruments, and syringe for hypodermic injection. Concentrations above 80 p.c. and below 60 p.c. are almost inactive since they do not penetrate proteins of bacteria readily.

Internally. **Stomach.**—As a **digestive stimulant,** alcohol may be given in small doses just before or during meals to (*a*) convalescents from acute illness with weakened appetite and digestion ; (*b*) patients suffering from chronic wasting diseases ; (*c*) old and overworked persons.

Iced champagne is valuable in sea sickness and in other forms of nausea and vomiting. Whisky or brandy with hot water often relieves gastric spasms and may be used as a carminative in flatulence and colic. Fainting, syncope, or threatening collapse may be averated by a single large dose of brandy or whisky by reflexly stimulating the circulation. Diarrhoea in the beginning may be checked by a stiff dose of brandy. Its use is contraindicated in gastric disorders and hyperacidity.

Heart.—As a **cardiac stimulant,** brandy or whisky is used in the threatening cardiac failure due to shock, haemorrhage, febrile and other diseases. Its value in shock is doubted by many careful observers ; and it is very difficult to assess the value of a drug in this condition. It is possible that it benefits by lessening anxiety and pain provided the patient is conscious. As a diffusible stimulant it acts purely reflexly, by increasing the pulse-rate, blood pressure and the respiration. This effect being of short duration it is used mainly as an emergency drug. The narcotic effect is also of value, since the psychic centres are not so easily excited and the medullary centres are less subject to dangerous shocks.

Nervous system.—Alcohol must be used with great caution in depressed conditions of the nervous system lest a bad habit be induced. Most nervous diseases do not require any alcohol. In some cases of insomnia, hysteria and neuralgia, alcohol no doubt affords temporary relief, but it must, if possible, be avoided for fear of generating intemperance. As to the use of alcohol in delirium tremens opinions differ. It should be withdrawn in the course of a few days. A sudden stoppage will precipitate the onset of delirium tremens. As a hypnotic alcohol may be used in mild insomnia due to overwork or mental strain at bedtime, either alone or with other simple hypnotics.

Fevers.—Alcohol was formerly almost invariably used in acute febrile diseases as a respiratory and circulatory stimulant, but its use has become very limited in recent years ; in fact most cases of fevers do well without it. It is only in exceptional cases and for limited periods that alcohol may be necessary to enable a patient to turn a critical corner. Its use is specially indicated in exhausting fevers, like typhoid, pneumonia and septic fevers. The beneficial effects are due not only because it acts as a food, but because it helps digestion of other foods. In wasting and exhausting diseases it tends to prevent excessive tissue waste and by acting as a narcotic allays nervousness and promotes sleep. Alcohol thus maintains the strength and nutrition of the patient, increases the output of the exhausted heart and makes it slower, regular and stronger. The tongue becomes moist, respiration less hurried, and in place of delirium the patient becomes quiet, free from excitement, and sleeps better so that strength is maintained. If alcohol fulfils these objects then it is doing good and its use should be maintained ; if not it should be discontinued. The action should be carefully watched to get the stimulant effect and not the depressant one.

Prescribing hints.—It must be borne in mind while ordering alcoholic beverages that the effects produced are modified by various circumstances ; such as (*a*) the amount of volatile ethers they contain ; this is of more importance than the actual alcoholic strength ; (*b*) the degree of their dilution with water ; (*c*) the age, toleration and habits as regards alcoholic drinks of the patient ; (*d*) the amount of exercise taken by him ; (*e*) the condition of his stomach, whether empty or full ; (*f*) the condition of the liver and the excretory organs, especially the kidneys ; and (*g*) the nature of the diseases for which they are given.

In many exhausting, febrile or other diseases, patients can consume without intoxication a large amount of alcohol. Sparkling wines (carbonic acid) facilitate absorption and produce a quicker action. Old brandy, whisky or port should be preferred as they contain less injurious ingredients. Children tolerate relatively larger quantities. In chronic diseases wines are more useful, but are liable to undergo fermentation in the stomach and are not so well-borne by some patients. Red wines usually disagree when there is hyperacidity. Owing to the presence of malt and diastase, beer produces obesity and aids digestion of carbohydrate foods.

Different varieties of wines should not be given at the same time, as they derange digestion. Small quantities in repeated doses with some easily digestible food are the best method of administration. Debilitated persons do well if an alcoholic drink is given an hour before food. Champagne, port, strong claret or beer may produce burning and aching of the rectum, and new and inferior brandy or whisky headache, because the latter contains fusel oil, furfural and many injurious aldehydes. It should be avoided where there is gastric irritation and when the kidneys are diseased on account of its effect on the renal epithelium.

2. General Anaesthetics and Narcotics

Narcosis is a "physiological condition in which the normal responsiveness or automatic activity of the living system—organism, tissue or cell—is temporarily decreased or abolished." Consciousness is the function of the cerebral cortex and drugs which produce unconsciousness are called *narcotics*, and unconsciousness however produced is always accompanied by some degree of reflex inhibition. Hypnotics in large over-doses often act as narcotics, *i.e.* cause a profound degree of unconsciousness. The difference between the two being one of degree. The rapidity of the onset of narcosis varies but the degree increases in a regular way with the amount given. In very small doses they produce a tendency to quietness, while in larger amounts they give rise to drowsiness, sleep, stupor, and finally loss of consciousness and coma. Narcotics therefore are used either to induce sleep or to produce surgical anaesthesia.

The narcotic effect of a drug persists as long as it remains in the blood in sufficient concentration, and no narcotic drug is known to get itself fixed in the brain cells so as to exert any late effects after the drug has been excreted from the general circulation. *Volatile narcotics* being rapidly absorbed and rapidly excreted by the lungs exert only a temporary effect ; wheareas the *non-volatile narcotics* are excreted *via* the kidney only to a limited extent and therefore maintain their effect for a longer period.

Since the chemical structure of the different narcotics have very little in common between them to explain their common effect, attempts have been made to explain their action as the result of some physical effect on the function of the brain cells exercised from outside rather than a chemical union with any of its components.

Meyer and Overton have advanced the theory of a close relationship between the narcotic action of these drugs and their relative solubility in oil as compared to water, *i.e.* a close parallelism between narcotic efficiency and partition coefficient, *i.e.*

$$\frac{\text{solubility in fat}}{\text{solubility in water}}$$

The higher this coefficient, the more powerful the narcotic action. They hold that all narcotic drugs are more soluble in fats and lipoids than in water. Thus when a narcotic drug enters the circulation it leaves the blood and since the nerve cells are rich in lipoids it accumulates in the brain and so alters the physical condition of the brain lipoids and interferes with their normal activity as to produce an anaesthetic effect. This effect is regarded as the function of the narcotics. The theory however applies to narcotics of the aliphatic series, *viz.*, chloroform, ether, chloral hydrate, etc., while morphine and other basic and saline narcotics like bromides, do not obey this law ; moreover, the peripheral nervous system though rich in lipoids is not affected by aliphatic narcotics.

Traube has shown a close relationship between the narcotic power of a drug and its power to lower surface tension to water. Here is again a similar parallelism between the surface tension effect and the partition coefficient, and it is not possible to say as to which property is the determining factor in narcosis. It is possible that both the factors participate to a varying extent in different tissues.

Since it is known that deprivation of oxygen, as in asphyxia, causes anaesthesia or narcosis, and that narcosis is followed by diminished oxygenation, Verworn and his associates have pointed out that deficiency of oxygen produces anaesthesia. They maintain that narcotics render the oxygen carriers of living tissues incapable of carrying oxygen. It is argued that diminished oxygenation may not be the cause of narcosis, but an effect of all narcosis which by suppressing irritability depress oxidation.

Quastel has shown that narcotics interfere with the power of brain tissue to utilise carbohydrate. It is possible that these drugs diminish the amount of available acetylcholine by retarding carbohydrate oxidation and thus prevent transmission of impulse at synapses in the central nervous system.

The real laws which govern the action of narcotics are not quite clear, and many carefully prepared substances have been found to possess totally different action from that anticipated. The reason why one drug acts as a narcotic than another is in many instances as obscure as is the cause which produces sleep or physiological narcosis.

The drugs of this group when used in sufficient concentration produce unconsciousness, muscular relaxation and abolition of all reflexes and pain so that operations can be performed without the patient feeling any pain. Most of these drugs belong to the aliphatic group, and being very volatile, some gaseous, they are rapidly absorbed by the lungs, therefore they are administered by inhalation. They

should be quickly eliminated from the system so that the patient will regain consciousness as quickly as possible after the anaesthetic is discontinued, at the same time they must produce these effects without depressing the vital centres dangerously, or causing any permanent damage to the central nervous system. The study of general anaesthetics means a knowledge of their toxicology, the patient being drugged into a state of narcosis approaching collapse.

Within recent years certain non-volatile substances are being extensively used for the production of general anaesthesia and narcosis. Those that are extensively used for the purpose are bromethol and the rapidly acting barbiturates, viz., hexobarbitone sodium, thiopentone sodium, pernocton (which contains bromine), sodium amytal and pentobarbitone sodium, (nembutal). But all are not suitable for all the routes. These are all soluble in water and are administered some by the mouth, others by the rectum, by intramuscular injection or by the intravenous route, the object being to produce partial narcosis, the anaesthesia being completed with some volatile or gaseous anaesthetic, or alternatively with a spinal or local anaesthetic. They belong to two groups, viz.—

(1) Alkaloidal narcotics, viz., hyoscine and morphine;
(2) paraldehyde, bromethol, derivatives of barbituric acid, and sulphate of magnesium.

These are used either for the production of general anaesthesia, or as **basal narcotics** preliminary to the use of volatile anaesthetics.

1. Volatile Anaesthetics

CHLOROFORMUM

Chloroform. (Chlorof.). $CHCl_3$

Source.—It is trichloromethane, to which 1 to 2 p.c. v/v of ethyl alcohol has been added.

Characters.—A colourless, volatile liquid; odour, characteristic; taste, sweet and burning. *Soluble* in 200 parts of water, miscible with dehydrated alcohol, with solvent ether, fixed and volatile oils, and with most organic solvents.

B. P. Dose.—1 to 5 ms. or 0.06 to 0.3 mil.

Official Preparations

1. **Aqua Chloroformi.**—0.25 p.c. **B. P. Dose.—1/2 to 1 oz. or 15 to 30 mils.**
2. **Spiritus Chloroformi,** *Syn.—Chloric Ether.*—5 p.c. **B. P. Dose.—5 to 30 ms. or 0.3 to 2 mils.**
3. **Emulsio Chloroformi.**—5 p. c. chloroform. **B. P. Dose.—5 to 30 ms. or 0.3 to 2 mils.**

Non-official Preparations

1. **Tinctura Chloroformi et Morphinae Co., B.P.C.**—A substitute for **chlorodyne.** Contains chloroform 3/4 m., morphine hydrochlor. 1/11 gr., acid. hydrocyan. dil. 1/2 m. in 10 ms. *Dose.*—5 to 15 ms. or 0.3 to 1 mil.
2. **Tinctura Chloroformi Co., B.P.C.**—Chloroform 10, alcohol (90 p.c.) 40, tinct. cardam. co. 50. *Dose.*—15 to 60 ms. or 1 to 4 mils.
3. **Linimentum Chloroformi, B.P.C.**—Chloroform and camphor liniment, equal **quantity.**

Pharmacology

Externally.—Chloroform when allowed to evaporate constricts the local blood vessels and paralyses the peri-

pheral sensory nerves, and is a **local anaesthetic.** If the evaporation is prevented, or if it be rubbed into the skin, it causes redness and even vesication. It is an **irritant,** more powerful than ether, a general protoplasmic poison, **and a powerful antiseptic.**

Internally.—The same irritant action is observed in the mouth and stomach when chloroform is taken internally. In diluted solution it has a warm sweetish taste and acts as a pleasant **carminative** and **stomachic.** It produces a sensation of warmth in the epigastrium and increases the vascularity and secretion of the stomach. Vomiting often accompanies anaesthesia and is central.

Heart and circulation.—Chloroform is quickly absorbed by the lungs and in concentrations used in anaesthesia depresses the muscles of the vessels, the splanchnic vessels being more affected than those of the extremities. It also **depresses the vaso-motor centre.** As a result of dilatation of the vessels and the depressed condition of the heart the blood pressure falls. The blood pressure is reduced from the beginning and the fall is very great in deep anaesthesia. The skin becomes pale and cold, pulse soft, slow but regular although there is quickening during the early stage from nervousness. Ordinarily the vaso-motor paralysis dominates and the heart beats efficiently even when the vaso-motor centre is paralysed.

The heart is very sensitive to chloroform, and experiments with isolated heart show that small amounts produce after a momentary slowing, depression, rendering the beats smaller and ineffective. A concentration of 0.015 p.c. of chloroform in the perfused fluid will arrest the heart. It is therefore a **direct poison to the cardiac muscle.** In prolonged anaesthesia the heart is affected directly supplemented by low blood pressure and asphyxia. During anaesthesia the heart may stop suddenly through rapid absorption of concentrated vapour and reflex vagus stimulation. It may occur in the early stage of the anaesthesia, or when the inhalation is irregular, or even after the inhalation has been stopped. Since it does not occur if the vagi are cut or an injection of atropine is given, it has been suggested that the stoppage is due to inhibitory stimulation. Others, chiefly Levy, explain it as the result of fibrillation brought on by excessive irritability of the muscle from chloroform vapour. It is possibly due to excessive sympathetic stimulation acting on an already irritable heart, or to an increased secretion of adrenaline.

Respiration.—In the early stage of anaesthesia the respiration is as a rule fairly regular, but deeper and quicker from stimulation of the centre ; this is followed by depression of the respiratory centre. If the inhalation is given in large amounts the breathing becomes irregular

from choking sensation and local irritation. During the stage of excitement it becomes more irregular, the patient holds his breath and then takes a few deep gasps allowing a large quantity of concentrated vapour into the blood. During the stage of anaesthesia the breathing becomes regular, though noisy, shallow and slow. If the administration is still prolonged it becomes stertorous, weaker and slower and eventually stops from paralysis of the centre.

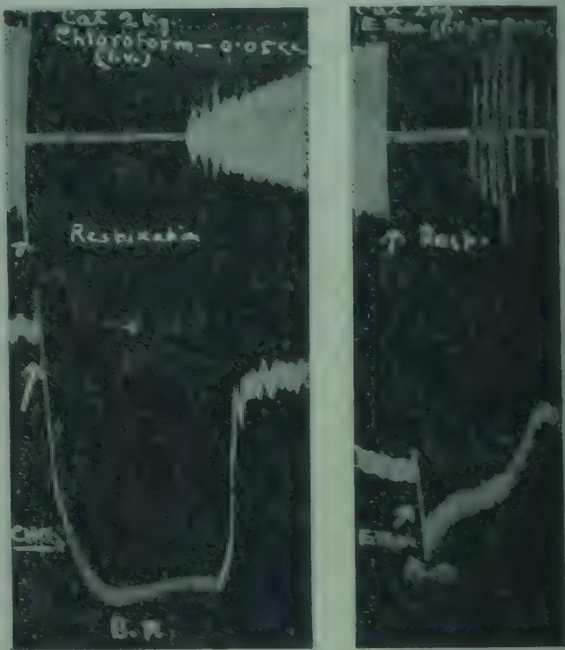


Fig. 3.—Cat under chloralose. Showing effect of small dose of chloroform (left) and ether (right) on blood pressure (lower) and respiration (upper). Note greater fall of blood pressure and more prolonged stoppage of respiration with chloroform : c.f. effects with ether (right).

The respiration may be temporarily stopped reflexly through irritation of the 5th nerve, *i.e.* through nasal mucous membrane. Reflex closure of the larynx, accumulation of mucus and saliva may also interfere with respiration. Anaesthesia of the larynx may lead to suction pneumonia, which is more common with ether than with chloroform. Direct irritation, haemorrhagic emboli or impurities in the anaesthetic used may also contribute to the formation of pneumonia.

Blood.—Both ether and chloroform when applied to drawn blood cause haemolysis but this effect is observed in a minor degree in life. Owing to the diminution of plasma there is polycythaemia, but the haemoglobin is reduced. In deep anaesthesia fibrinogen disappears from the blood thus diminishing its coagulability. This effect is possibly due to derangement of the liver and disappears with its repair.

Eye.—Its effect on the eye varies in different stages and depends upon the amount used. At first the pupil is dilated from stimulation of the sympathetic, though light

reflex remains intact. Later there is contraction from stimulation of the oculo-motor centre and paralysis of the sympathetic. During profound anaesthesia the pupils dilate from paralysis of the centre and the reaction to light is also lost. This implies either (*a*) overdose, (*b*) asphyxia, or (*c*) reflex from operative procedure. In patients who receive either morphine or atropine or both before anaesthesia, the pupillary reaction may not be very marked.

Kidneys.—During anaesthesia the secretion of urine is diminished. Albumin appears, and in some cases fatty degeneration and permanent inflammatory lesions of the kidneys have been observed.

Therapeutics

Externally.—As a local anodyne, chloroform may be combined with liniments of aconite and belladonna (A. B. C. liniment) and applied in myalgia, lumbago, chronic rheumatism, etc. If counter-irritation is required the liniment may be sprinkled over a piece of cloth or lint and covered with oiled silk.

Internally.—A pellet of cotton wool soaked in chloroform and introduced into the cavity of a painful carious tooth relieves **toothache.** One or two drops may check vomiting, sea-sickness and flatulent distension. In diarrhoea or in the beginning of cholera spirit of chloroform may be usefully combined with opium or other astringents. Chlorodyne is a useful remedy in these cases. It is also useful in intestinal and other **colics.**

A deep hypodermic injection (10 ms.) near the sciatic nerve relieves sciatica.

AETHER SOLVENS
(Aether Solv.)

Syn.—Ethyl Oxide ; Ethylic Ether ; Sulphuric Ether. $(C_2H_5)_2O$.

Source.—Solvent Ether is diethyl ether and is obtained by distilling a mixture of ethyl alcohol and sulphuric acid, rectifying the distillate.

Characters.—Same as ether.
Enters into.—Collodium Flexile.

Aether Anaestheticus. *Syn.—Ether.*—Anaesthetic Ether is purified diethyl ether, to which may be added a suitable stabiliser in a proportion not greater than 0.002 p.c.

Characters.—A colourless, transparent, very mobile liquid ; odour, characteristic ; taste, sweet and burning. Very volatile and inflammable. *Soluble* in 6.5 volumes of water ; miscible in all proportions with alcohol (90 p. c.), chloroform, fixed and volatile oils.

Official Preparation

1. **Spiritus Aetheris.**—Contains 33 p.c. ether. **B. P. Dose.—15 to 60 ms. or 1 to 4 mils.**

Non-official Preparation

1. **Spiritus Aetheris Co., B.P.C.** *Syn. Hoffmann's Anodyne.*—Ether 137.5 mil, alcohol (90 p.c.) 1656.6 mil, sulphuric acid 900.0 mil, water 37.5 mil, sodium borate, q.s. *Dose.*—20 to 40 ms. or 1.3 to 2.6 mils ; 60 to 90 ms, or 4 to 6 mils (Single Dose).

Pharmacology

Externally.—Being extremely volatile, ether cools the skin and even freezes the part so that if applied as a spray it produces **local anaesthesia.** The cooling is followed by burning. If evaporation is prevented, it acts as an irritant and even vesicant. It is a powerful **antiseptic.**

Internally.—It produces burning, a disagreeable and characteristic taste in the mouth and reflexly stimulates the secretion of saliva. In the stomach it is quickly absorbed, increases gastric secretion, expels gas and acts as a gastric stimulant and **carminative** and reflexly stimulates the heart. It is also a valuable intestinal antispasmodic.

Heart and circulation.—Whether administered by the mouth, hypodermically or as inhalation, ether stimulates the heart and causes a **rise of blood pressure.** These effects are reflex through stimulation of the accelerator and vaso-motor centres. The heart is also **directly stimulated.** Whereas a concentration of 0.015 p.c. of chloroform in the perfused fluid will arrest a mammalian heart, a concentration of 0.4 p.c. of ether is necessary to produce the same effect. In the early stage of the anaesthesia the pulse is quickened and the blood pressure is raised. During anaesthesia the cerebral and skin vessels are dilated but the intestinal vessels are constricted and the pressure remains unaltered. During the paralytic stage the vaso-motor centre is depressed, and the blood pressure falls slowly. The heart remains normal even after the stoppage of respiration.

Respiration.—At first respiration becomes quicker and deeper through reflex stimulation from mouth, stomach and the respiratory passages. Large doses, as when given to produce anaesthesia, depress the respiratory centre, death being due to asphyxia from respiratory paralysis.

Uterus.—Moderate anaesthesia has little effect on the uterine contractions, although cases of death of the foetus under ether or chloroform during labour are on record. This may be due either to a direct action on the foetus or to asphyxia from low maternal blood pressure.

Kidneys.—During the anaesthetic stage the secretion of urine is diminished from constriction of the renal vessels ; after this stage is over there is profuse diuresis. Albumin appears in the urine, which however soon passes off, though nephritis with albumin and even blood in the urine may appear in some cases.

Therapeutics

Externally.—For superficial minor operations, ether used as a spray produces sufficient anaesthesia for the purpose. As this effect does not extend into the deeper

tissues, it is not suitable for deep surgical operations. It is used as an antiseptic for infected wounds.

Internally.—As a **carminative** and **antispasmodic,** ether is useful in some forms of dyspepsia, gastrodynia, and intestinal cramps. Hoffmann's anodyne is an excellent combination for the relief of intestinal and biliary colic, and in hiccough when used with ice.

Heart and lungs.—It is a valuable cardiac and respiratory stimulant when given by the mouth (10 to 40 ms.) or hypodermically (10 to 40 ms. dissolved in olive oil) in syncope, fainting and cardiac failure from any cause.* Its effects are transient and it has to be repeated. It is also useful in angina and spasmodic bronchitis.

ETHER AND CHLOROFORM AS GENERAL ANAESTHETICS

Both ether and chloroform when inhaled produce general anaesthesia by their action on the central nervous system. This action may be conveniently described under *four stages,* as follows :—

First Stage or that of imperfect consciousness.—This begins with a feeling of warmth on the surface, sounds in the head, flashes of light before the eyes, choking or suffocation, or sometimes cough (especially if the vapour is concentrated), and confusion of ideas. Sounds are faintly heard, questions are imperfectly answered and pain, if present, is not much felt, indicating a blunting of the general sensibility. As a result of irritation, lachrymation, salivation and excessive secretion of mucus occur.

Second Stage or that of general stimulation.—The patient is no longer conscious of external impressions, and loses control over himself, so that according to temperament, he may sing, cry, shout, or struggle (hence some authors call this "the struggling stage"). Excitment is common with muscular people and heavy drinkers. In fact different people behave differently during this stage. At times the struggling is so hard that the patient holds his breath, the face becomes livid, the eyes protrude and the jugular veins distend. Almost coincidently the lower centres are stimulated ; the pulse becomes frequent, the heart and large vessels throb, respiration becomes quickened, blood pressure rises and the pupils become slightly dilated through stimulation of the sympathetic possibly due to increased secretion of adrenaline due to excitement. If the eyes are inspected they will be found to be moving from side to side or fixed eccentrically. This condition of the eye persists in the first plane of the third stage. The

*Sp. ammon. aromat.	ms.	30
Sp. ether.	ms.	20
Sp. chlorof.	ms.	15
Tinct. cardam. co.	ms.	60
Aq. camph.	ad. oz.	1
A diffusible stimulant		

respiratory reflexes become exaggerated, and may even cause through irritating vapour spasmodic arrest, coughing and alternating periods of shallow and deep breathing causing an uneven absorption of the anaesthetic. After a period of apnoea the patient takes a few deep breaths causing a dangerously high concentration of the anaesthetic into the circulation. All the reflexes are present in this stage, *e.g.* vomiting, coughing and conjunctival reflex, and reaction of the pupil to light.

Third Stage or that of surgical anaesthesia.—This is characterised by the paralysis of the nerve-centres which have previously been excited, and the abolition of reflex action and sensation.

First plane.—The onset of this stage is marked by respiratory movement becoming regular and deep as in normal sleep. The eyeballs still show marked movements (rolling of eyeballs) but as the anaesthesia progresses these become more sluggish and eventually become fixed centrally. The time when the fixation takes place is arbitrarily regarded as the line between the first plane and second plane of the third stage.

Second plane.—If the inhalation is continued, the the patient becomes completely unconscious. The notable feature of this stage is the progressive loss of tone of the muscles ; his limbs become flaccid, and if one of them is held up it falls like that of a corpse, the neck muscles relax and the head can be turned easily to either side. But the most significant sign is that the abdominal recti muscles gradually become less prominent and feel less resistant on palpation. Only a sluggish contraction of the iris follows when the eyes are suddenly exposed to the light, but the peritoneal reflex is still present and it may be necessary to push the anaesthetic for a few minutes to bring the patient to the third plane. The *pupils are contracted* through stimulation of the oculo-motor centre and paralysis of the sympathetic and the conjunctival reflex is completely abolished.

Third plane.—Anaesthesia carried on to the lower border of the second plane is sufficient for most operations. If however the anaesthesia is further continued the third plane is reached which is heralded by diminished respiratory movements of the chest and increased movement of the diaphragm, *i.e.* the respiration becomes abdominal. This is a sign of respiratory failure, the eyeballs are fixed in convergence and the *pupils begin to dilate.*

Fourth plane.—In this plane the pulse falls in volume and becomes irregular and rapid, respiration becomes slow, deep and stertorous and the blood pressure falls from paralysis of the vaso-motor centre.

Fourth stage or that of bulbar paralysis and collapse.—If the anaesthetic is pushed further, the lowest reflex centres are paralysed causing complete loss of muscular tone, and the patient passes urine and stool involuntarily. The patient's face becomes pallid, or may be deeply cyanosed. The *pupils dilate* widely which is an indication of commencing asphyxia and of the paralysis of vaso-motor, respiratory and cardiac centres. It is therefore an important *danger signal.* The blood vessels and capillaries dilate and the blood pressure falls to zero. Eventually the respiration fails before the arrest of the heart which stops in diastole.

Complications of General Anaesthesia

A. **Dangers during administration.**

1. **Respiration.**—This may be due to any of the following causes :—

(*a*) *Obstruction of the glottis* by falling back of the tongue or the sucking in of vomited matter or blood.

(*b*) *Spasm of the glottis* from the inhalation of vapour, which is either too strong or contains irritating products of decomposition.

(*c*) *Mechanical impediments to respiration,* due either to (1) *constrained position of the patient* as in obstetric and renal operations ; (2) *pressure of tight clothes or bandages,* or the *assistant's arms* ; (3) *falling in of the lips and alae nasi,* as in old people who have lost their teeth ; (4) *spasmodic holding of the breath* especially in nervous patients, and during the early stages of the administration.

(*d*) *Paralysis of respiration* occurs more often from ether than from chloroform, where deaths are due more from cardiac shock. If chloroform or ether is used freely diluted, the respiration stops before the heart, in more concentrated forms the heart continues to beat for a very short time. It is possible that the failure of respiration may be the effect of anaemia of the central nervous system from fall of blood pressure. Weakness of the heart therefore only indirectly affects respiration.

(*e*) *Reflex irritation of the fifth nerve* through nasal mucous membrane may cause temporary stoppage of respiration. Accumulation of mucus or saliva may also interfere with respiration.

2. **Heart.**—Death from stoppage of the heart may occur from :—

(*a*) *Excessive concentration of chloroform vapour* causing sudden paralysis of the cardiac muscle. The lung surface of absorption is extensive, hence a very concentrated dose passes into the heart quickly which has a toxic action on the myocardium.

(*b*) *Stimulation of the vagus centre.*—This may be reflex from the nose, larynx, trachea, or from the pulmonary irritation by the concentrated vapour. This may happen even in trivial operation, specially if the anaesthesia is incomplete. This is avoided by injection of atropine.

(*c*) *Peripheral resistance.*—From excessive reflex vaso-constriction.

(*d*) *Overaction of the sympathetic*, causing fibrillation of the heart, due to increased output of adrenaline. This frequently occurs in nervous patients whose blood contains excess of adrenaline, and the heart becomes highly sensitive to chloroform. A sensory stimulus acts as an exciting factor and with additional secretion of adrenaline produces fibrillation and arrest of the heart.

(*e*) *Diseases of the heart.*—The heart is apt to fail if it is fatty, dilated or structurally disorganised. This happens with chloroform, when used in old, the infirm, the anaemic, drunkards, epileptics and those who suffer from valvular diseases. For these people ether is the safer anaesthetic.

(*f*) *Pressure on the carotid sinus.*—Since external compression of the carotid sinus stimulates the adventitial sensory nerve-endings and reflexly slows the heart, or sometimes may cause complete arrest of the heart, it is possible that the nerve connections of the sinus and the effect of pressure on it may have some connection with the sudden stoppage of the heart.

B. Dangers after operation (late symptoms).

(*a*) *Vomiting.*—When slight it is of no consequence and is a sign of reaction from shock after operation. Sometimes it may be severe, and may be due to (*i*) idiosyncrasy or digestive disturbances, (*ii*) central effect, and (*iii*) excessive dose of chloroform. In the early stage vomiting is due to the taste and smell of the vapour.

(*b*) *Bronchitis and complication of the lungs.*—These occur chiefly from the use of ether which irritates the bronchi, and in susceptible persons may set up bronchitis. It may even cause severe and fatal bronchial complications in persons suffering from pulmonary congestion, from septic inhaler.

(*c*) *Acid intoxication.*—Administration of any lipoid soluble anaesthetic reduces the alkali reserve of the blood specially if the administration is prolonged. This may appear within a few hours to six days after the use of the anaesthetic. The symptoms are those of acute acidosis ; there is persistent vomiting, fatty degeneration of the liver, heart and kidneys, leading to toxaemia, icterus, pros-

tration, coma and death. This is known as *delayed chloroform poisoning*. The danger is greater in conditions associated with acidosis, *e.g.* in diabetes, eclampsia, vomiting of pregnancy, acute yellow atrophy of the liver, etc. In these conditions the use of glucose and bicarbonate of soda before starting the operation should be considered.

(*d*) *Renal irritation.*—In a certain percentage of cases, more with chloroform than with ether, albumin appears in the urine with casts. This usually disappears in persons with healthy kidneys, but in persons with diseased kidneys there may be fatal suppression of urine and occasionally fatty degeneration.

(*e*) *Troublesome flatulence and post-operative gastric and intestinal paralysis.*—These are more common with ether. The relaxation of the gastric muscles favours dilatation of the stomach and irregular peristalsis, which are responsible for the "gas pains" so common with ether. Sometimes there may be spastic contraction of the colon with accumulation of gas and fluid above.

Recovery from anaesthesia.—The rapidity of recovery depends upon the amount of anaesthetic used and on the duration of administration. If after full anaesthesia the patient is just kept under with a few whiffs now and then, recovery takes place very soon after the administration is stopped. The lowest functions reappear first, the respiration becomes quieter, the eye reflex and deglutition reflex appear next, then after a while consciousness returns. The mental equilibrium is established last. Coughing, retching and vomiting appear with return of consciousness.

Absorption and clearance.—Both ether and chloroform are absorbed and eliminated very quickly from the lungs, only a small part being excreted by the urine. At the beginning the amount excreted, *i.e.* in the expired air, is much less than in the inspired air, showing that there is retention of the anaesthetic in the body. They exist in the blood and tissues chiefly in physical solution, and are therefore absorbed and excreted by the alveolar blood in proportion to their concentration in the alveolar air. With ether, light anaesthesia can be obtained at a concentration of 6 p.c. by volume of ether vapour, while deep anaesthesia requires 10.5 p.c. by volume. Fatal concentration with ether is 11 p.c. For chloroform, the corresponding concentrations are 1.35 volume p.c. for light anaesthesia, and 1.65 p.c. for deep anaesthesia, and fatal concentration is 2 p.c. (Sollmann). The *margin of safety* between minimal anaesthetic and fatal dose therefore is greater with ether than with chloroform.

Cases unsuitable for chloroform.—Those suffering from anaemia, low blood pressure, cachexia, angina, weak and fatty heart, Graves' disease, haemorrhage and ade-

noids. Diabetics and any condition that favours acidosis, and those suffering from jaundice are also bad subjects.

Cases unsuitable for ether.—Those suffering from laryngeal spasm or obstruction, and any disease of the lungs or pleura. Very old age, those suffering from atheroma, aortic aneurism and renal disease, and operations with cautery near the mouth are contra-indications for ether.

Accumulation of mucus or saliva often gives trouble by blocking the air way, and is more marked with ether. This is obviated by giving a preliminary injection of atropine, or by turning the head to one side to help drainage, or by swabbing out the mucus with mops. During the stage of muscular relaxation the falling back of the tongue obstructs the air passage.

Uses of general anaesthetics.—These are chiefly restricted to cases where surgical operations or manipulations are required and which will involve much pain and suffering to the patient. They are therefore used to annul pain and produce unconsciousness. Their field of usefulness has however within recent years become limited owing to our advance in knowledge regarding the different local anaesthetics, and the various improvements introduced with regard to their uses. In fact many operations which were formerly performed under general anaesthesia are now done with local anaesthetics with much success. There are however certain limitations to the use of local anaesthetics. Where complete relaxation of the muscles is essential to the success of the operation, or where any movement on the part of the patient may interfere with the success of the operation, or where we want to avoid any depressing effect associated with the operation in a nervous patient, chloroform and ether will continue to hold their field. Besides surgical operations they may be used under the following conditions :—

1. *To produce anaesthesia of slight degree during labour* with moderate inhalation after full dilatation of the os. Deep anaesthesia is as a rule not required and only prolongs labour.

2. *To relax muscular spasm* during the reduction of dislocations or hernias, the setting up of fractures, or during catheterisation.

3. *For the purpose of diagnosis*, as in the case of young children or hysterical subjects. For the examination of abdominal viscera or to ascertain whether a particular swelling is a real or a phantom tumour.

4. *To relieve the intense pain of certain diseases*, such as biliary, intestinal and renal colics, neuralgias, etc.

5. *To relieve the spasms* of many convulsive diseases, such as tetanus, strychnine poisoning, hydrophobia, etc.

Preparation of the patient.—During an emergency it is not possible to prepare the patient adequately, and it is surprising that as a rule no untoward result follows the use of an anaesthetic. Even under normal conditions the drastic methods of preparation followed before are avoided. The patient is given a preliminary purge, preferably castor oil, 36 hours before operation, and an enema on the evening before. Sometimes a rectal wash is given a few hours before the operation, but this weakens the patient and is not necessary except in cases of rectal operation. The patient should be kept on light food on the previous day, and no food is given on the morning of the operation to keep the stomach empty and avoid vomiting. A cup of tea and a slice of toast may however be given if necessary. Glucose or some form of sugar is of great service to replenish the carbohydrate reserve of the body and as a *preventive against post anaesthetic vomiting and acidosis.* An injection of atropine is given as a routine method to prevent excessive perspiration, secretion of mucus and reflex vagus stimulation. It is more indicated when ether is used and should be given in full doses.

Administration of chloroform.—The essential feature in the administration of chloroform is to avoid the danger of over concentration of the vapour or of surcharging the blood by too rapid administration.

The following practical hints should be particularly attended to while administering chloroform :—

1. Chloroform should be perfectly pure. The A. C. (alcohol and chloroform) mixture or A.C.E. (alcohol, chloroform and ether) mixture is only indicated in cases where there is a fatty or weak heart, or where the operation is likely to be a protracted one.
2. All tight clothes about the neck, chest and abdomen should be removed or materially loosened. Attendant's or dresser's hands should not press upon the chest or abdomen while holding the patient.
3. Artificial teeth should be removed.
4. The safest position of the patient is the dorsal decubitus.
5. As the undivided attention of the anaesthetist is essential for the safety of the patient, the operator should not undertake to administer the chloroform and to operate at the same time.
6. Chloroform should be freely diluted with air.
7. An ordinary handkerchief or a piece of lint folded in the form of an open cone within which some absorbent cotton has been stitched is the best inhaler in the absence of Junker's apparatus, which does not allow a greater concentration of chloroform than 5 per cent. If a cone is used it should not be held either too close to or too distant from the mouth and the nose. The proper distance throughout the inhalation is the nearest which does not cause choking, struggling or holding of breath.
8. If the patient is weak, a small dose of brandy or whisky may with advantage be given before the inhalation is begun. A nervous patient should be brought into a calm state of mind as far as possible and an injection of morphine may be considered (*see* Basal Narcosis).
9. If lint is used, not more than 20 or 30 ms. should be sprinkled on to it at a time. Some anaesthetists prefer to commence with double this dose, so as to lessen the period of excitement.
10. Pay particular attention to the breathing, as most of the accidents are caused by respiratory failure. Irregularity of breathing is generally caused by insufficiency of air, which makes the patient struggle, or hold his breath.
11. No operation should be commenced until the patient is under complete anaesthesia, as shown by the absence of the corneal reflex. The administration should never be pushed to the stage of

stertorous breathing and complete relaxation of muscles, except when it is absolutely necessary as for the reduction of old-standing dislocations.

12. Directly the corneal sensibility is lost or respiration becomes stertorous, the inhalation must be suspended. In case the stertor comes on while the cornea is still sensitive the inhalation should not be proceeded with, as it invariably happens that the cornea becomes insensitive within a few seconds afterwards.

13. The patient's head should be turned to one side, the lower jaw depressed and the tongue drawn forward if necessary during vomiting, so that no vomited matter may enter the larynx. Should this accident happen laryngotomy must be at once performed.

14. Special care should be taken during an operation on the mouth to prevent any blood flowing down into the larynx. Full anaesthesia may be maintained by introducing chloroform vapour into the post-nasal space through a soft catheter connected with the Junker's inhaler.

15. Lividity of the face and deep stertor indicate lack of oxygen and should at once be controlled by stopping the anaesthetic, raising the shoulder, opening the mouth and pulling out the tongue to enable the patient to breathe more air ; at the same time all mucus should be removed to clear the air way.

Treatment of untoward symptoms.—(a) *Cyanosis.*—When due to obstruction of the air way, as by excessive secretion, falling back of the tongue, etc., this should be rectified without delay. When due to respiratory weakness, it demands immediate withdrawal of the anaesthetic, use of artificial respiration and administration of respiratory stimulants, e.g. atropine, strychnine, caffeine, leptazol, nikethamide, and inhalation of 5 p.c. CO_2 with oxygen. It is however very doubtful if any of these drugs are of any use when the circulation is so feeble that the drug cannot reach the vital centres to stimulate either the respiratory centre or the heart.

(b) *Weak and irregular pulse* should be treated by stoppage of further anaesthetic and administration of saline, either per rectum or intravenously, depending upon the urgency of the case.

(c) *Collapse.*—(i) In ether anaesthesia, whatever may be the stage of operation, it should be suspended and the patient put into Trendelenburg position. If from chloroform, keep the body level.

(ii) Lungs should be slowly and rhythmically inflated with CO_2 and oxygen (10 p.c. and 90 p.c.), or with pure oxygen.

(iii) Hot blanket to keep the body warm, and if necessary, the limbs may be bandaged from fingers upwards.

(iv) Injection of atropine or caffeine in ether anaesthesia, and cardiac stimulants in chloroform collapse, *e. g.* camphor, nikethamide or leptazol.

(v) Heart failure may be treated with injections of strychnine, camphor or glucose. But since all these drugs act in diverse ways, it has been suggested that the stimulation caused by the needle brings on recovery. Cardiac massage may also be tried. Since adrenaline favours fibrillation, it should not be used in cardiac syncope.

Carbonic acid gas in anaesthesia.—This gas being the natural and efficient respiratory stimulant is of great use to the anaesthetist, and when used with oxygen it hastens the induction of anaesthesia by stimulating breathing. At the end of the anaesthesia it will help the elimination of the anaesthetic and thus lessen post anaesthetic complications. Besides preventing respiratory failure it counteracts shock. It is used in strength of 5 p.c. with oxygen.

Treatment after inhalation.—No food should be given for at least two hours after inhalation. Iced soups or jellies and iced milk with soda water may be given during the next 12 hours. Vomiting

may be checked by the sucking of lumps of ice or by a teaspoonful of burnt brandy.

Method of administration of ether.—The routine method is by inhalation either by the open or closed method. The open method is safer but more anaesthetic is required and it takes a longer time to produce anaesthesia. Buxton recommends inhalation of ether with oxygen in cases where the introduction presents difficulties from spasm, cough, holding of breath, struggling with cyanosis, in alcoholics and in persons with weak vitality. Hewitt and Blumfeld advocate the administration of ether 3 parts, and chloroform 2 parts by volume by the open method (Skinner's mask) to the exclusion of all other methods on account of its alleged safety and freedom from after-effects.

Recently ether is administered per rectum dissolved in equal volume of olive oil, and may be combined with paraldehyde or chlorbutol. Ether 2 to 5 oz., olive oil 2 to 4 oz., and paraldehyde 2 to 4 drs. form a suitable dose for an adult, depending upon the physique and depth of anaesthesia required. This is introduced by a siphon tube 20 minutes before the operation after emptying the rectum with a purgative followed by an enema. An hour before the operation a dose of morphine, or atropine and scopolamine is given. When the operation is over, the unabsorbed portion is siphoned off and the bowel washed out with soap and water enema. This method spares the respiratory tract so that there is less salivary and bronchial secretion and there is less vomiting and nausea. It is especially indicated in operations about the mouth and throat. But the anaesthesia is not under full control, and may be followed by irritation and even haemorrhage from the bowels. A few cases of death have been recorded in children possibly due to overdosage, or to absorption of an excessive quantity from unhealthy condition of the rectum.

Ether and other gas anaesthetics are often administered by closed circuit apparatus with the result that the patient rebreathes his own expired air. This should not be allowed unless the exhaled carbon dioxide is neutralised, and oxygen sufficient to satisfy the patient's metabolic needs is supplied. An apparatus therefore should be equipped with the means of absorbing carbon dioxide and supplying oxygen in measured quantity by continuous flow. For absorption of CO_2 soda lime is used (*see* page 103).

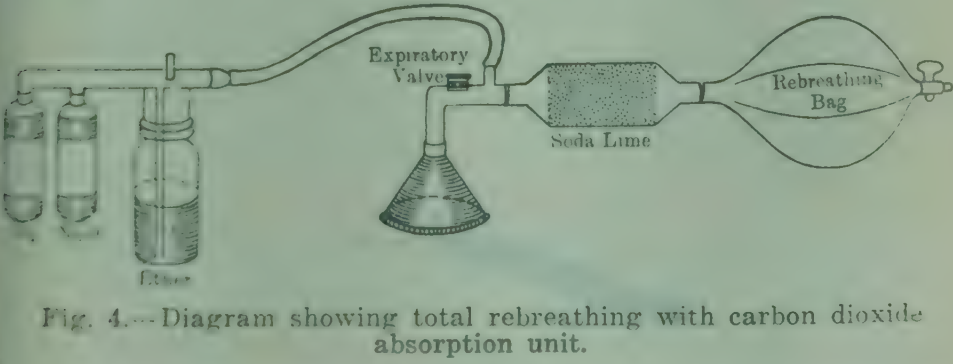


Fig. 4.—Diagram showing total rebreathing with carbon dioxide absorption unit.

Choice of anaesthetics.—There is a wide range of anaesthetics, both local and general, for the surgeon to make his selection from. The indications for both ether and chloroform have been fully discussed. It is only necessary to point out that in both cases the drug must be pure. Chloroform would have been the ideal anaesthetic if it were safe. It is portable, and least bulky of all the anaesthetics and never fails to anaesthetise. It causes less irritation and less feeling of suffocation. On the other hand ether is rather more than

twice as safe as chloroform. Where however irritation of the air passages is apprehended and muscular relaxation is required, chloroform should get the preference. For short operations the choice should be for gas and ethyl chloride, and for prolonged operation, gas, oxygen and ether. The choice of an anaesthetic will depend upon (1) the patient's physique, condition, age and mentality; (2) the surgeon's requirements; and (3) the length and nature of the operation. If the anaesthesia requires to be prolonged, a combination of nitrous oxide, chloroform and ether, or alcohol, chloroform and ether may be selected. In cases where the heart is weak or otherwise diseased, ether should be preferred and chloroform avoided. But if damage to the heart is great, ether should also be avoided as being dangerous on account of the strain on the damaged heart during excitement. Active bronchitis or indeed a moist chest of any sort should preclude the use of ether. Children are especially susceptible to ether irritation and it is not suitable for operation about the mouth and larynx. Sometimes a few whiffs of nitrous oxide gas makes ether more pleasant.

The differences between chloroform and ether are tabulated below :—

Ether	Chloroform
1. Ether is a weaker anaesthetic and should be used in a concentrated form; 6 p.c. by volume or 15 p.c. by weight.	Chloroform must be given well diluted; 97 to 98 p.c. of air and 2 to 3 p.c. of chloroform.
2. Ether being inflammable, no fire should be brought close to the mouth.	Chloroform is not inflammable.
3. A large quantity (several ounces) is needed to produce anaesthesia.	A small quantity, 3 drs. to 1 oz. is enough.
4. The smell of ether is disagreeable.	The smell of chloroform is not disagreeable.
5. The stage of stimulation is very much protracted and there is more struggling.	The stage of stimulation is shorter and therefore less struggling.
6. The stage of anaesthesia is shorter, and the degree of anaesthesia is less profound.	The stage of anaesthesia is more complete, and the degree more profound.
7. The fall of temperature is great.	The fall of temperature is slight.
8. Nausea and vomiting common after-effects.	Nausea and vomiting less common after-effects.
9. Muscular relaxation not so easily produced.	Muscular relaxation easily produced.
10. Not toxic to liver and kidneys.	Toxic to liver and kidneys.
11. Cardiac, respiratory, and vasomotor centres are not readily paralysed; hence ether is a *safer* anaesthetic.	Cardiac, respiratory and vaso-motor centres are readily paralysed, hence chloroform is *not* so safe an anaesthetic.
12. Bronchial and lung complications such as bronchitis, pneumonia are frequent.	Bronchial and lung complications are uncommon.
13. Elimination is slow and the smell hangs about the body for a long period.	Elimination is rapid and the smell does not hang about so long.
14. Death from syncope during inhalation is less probable in subjects of cardiac weakness.	Death from syncope is more probable in subjects of cardiac weakness.

AETHYLIS CHLORIDUM. (Aethyl. Chlor.). C_2H_5Cl.—Ethyl Chloride is obtained by the action of hydrogen chloride on ethyl alcohol or on Industrial Methylated Spirit.

Characters.—Gaseous at ordinary temperatures and pressures, but as usually supplied is condensed into colourless, mobile, inflammable, and very volatile liquid. *Odour*, pleasant and ethereal. Slightly *soluble* in water, miscible with alcohol (90 p. c.), and with solvent ether.

Pharmacology and Therapeutics

Ethyl chloride is both a local and general anaesthetic, and being extremely volatile is largely used in the form of spray to produce local anaesthesia in **dental practice** and **minor surgery.** As this anaesthesia does not penetrate into the deeper tissue it cannot be used for deep surgical

operations. When inhaled it induces anaesthesia within half to two minutes and recovery occurs within a few minutes. The blood pressure falls, due partly to the depressed action of the heart and to the relaxation of the blood-vessels. Being very volatile it is administered in a concentrated form, for this purpose a mask similar to that used for nitrous oxide gas may be used. An ordinary glass funnel with some loose absorbent cotton-wool serves the purpose equally well ; the broad end being placed over the mouth, ethyl chloride is sprayed upon the cotton through the small end. Excepting in children, corneal reflex is not lost and that it is not of much value when muscular relaxation is required. Ethyl chloride is a comparatively safe anaesthetic and may be used to induce anaesthesia which is maintained by administration of ether or chloroform. It is contra-indicated in serious diseases of the heart and myocardial degeneration, where ether is safer.

AETHER VINYLICUS. (Aether Vinyl.). $(CH_2 : CH)_2 O$. Syn.—*Vinethene.*—Vinyl Ether is divinyl ether to which has been added about 4 p.c. v/v of dehydrated alcohol, and not more than 0.01 p.c. w/v of phenyl-*a*-naphthylamine or other stabiliser.

Characters.—A clear, colourless, inflammable liquid often with a purplish fluorescence ; odour, characteristic. *Soluble* at 15.5°, in about 100 parts of water. Miscible in all proportions with alcohol (90 p.c.), with solvent ether, and with chloroform.

Action and Uses

It is a powerful anaesthetic, its potency being four times that of ether, and is inflammable. Anaesthesia is produced very quickly, within 1/2 to 1 minute with little excitement. It does not irritate the respiratory passages nor impair circulation and respiration. Any degree of muscular relaxation can be obtained with it. Recovery is very rapid. The relative safety of this anaesthetic over ether is still unsettled, and cases are on record where it produced damage to the liver after prolonged anaesthesia. As a rule there is no post-operative nausea and vomiting, and unlike ether pulmonary sequelae are very rare. Owing to the rapid action, ease of administration and comparative safety to the mother and the child it is suitable in obstetric practice. Best administered by the closed method with oxygen, although open drop method can be used for short period, not longer than one hour. A mixture of vinyl ether 1 part with ether 3 parts, administered by the open method, induces rapid anaesthesia with sufficient muscular relaxation for short operation.

Contraindications.—(a) When there is risk of inflammability, (b) damaged liver, (c) prolonged anaesthesia, *i. e.* more than 30 minutes, except as an adjuvant.

TRICHLOROAETHYLENUM. (Trichloroaethylen.).—$CHCl : CCl_2$.

Trichloroethylene may be prepared by the chlorination of acetylene to give tetrachloroethane followed by treatment with lime and purification by distillation. Thymol 0.01 p.c. w/v may be added as a preservative.

Characters.—A colourless, transparent, mobile liquid ; odour characteristic, resembling that of chloroform ; taste, sweet and burning. Slowly decomposes on exposure to bright light in the presence of air. Almost *insoluble* in water, miscible with dehydrated alcohol, with solvent ether, with chloroform and with fixed and volatile oils.

Action and Uses

It resembles chloroform in its effects but is less potent and les toxic, the margin of safety being much higher. It however produ ces more marked analgesia. Its action is smooth and quick speci ally when given with oxygen and nitrous oxide. Effective concen tration in the blood during anaesthesia is 6 to 12 mg. per 100 c.c It is non-inflammable, causes less superficial oozing, and produce little or no irritation of the upper air passages. It is not alway possible to get surgical relaxation and in such cases it should not b pushed further but should change over to ether.

It may be administered by the open method, but being less vola tile renders the method unsatisfactory. For the same reason it excretion is slow and therefore recovery is also slow.

It is valuable in minor surgery, obstetric practice, when dia thermy is used, and in major surgery when deep plane of anaesthe sia is not required.

Advantages.—(a) High analgesic quality, (b) non-inflammable (c) smooth induction, (d) absence of nausea and vomiting, (e) les capillary oozing.

Caution.—It should not be used in a closed circuit apparatu with CO_2 absorption technique as the presence of alkali and hea generated causes destruction of trichloroethylene with productio of a dangerous toxic compound dichloracetylene. A case of fata necrosis of the liver has been recorded and repeated administratio within a short period should be avoided.

2. Anaesthetic Gases

AETHYLENUM. (Aethylen.). $CH_2 : CH_2$. **Syn.**—Olefiant Gas.— Ethylene contains not less than 98 p. c. v/v of ethylene. It may b compressed in metal cylinders.

Characters.—A colourless, inflammable gas, with a slightly sweet odour an taste. One volume dissolves in 9.2 volumes of water, in about half a volume o alcohol (95 p. c.) at 25°C., and in about 0.05 volume of solvent ether at 15.5°C.

Pharmacology and Therapeutics

At ordinary temperature and pressure ethylene exist as a gas and induces *general anaesthesia* when inhale with oxygen. The effects are similar to those of ethe which it resembles, but more rapid in onset, in which res pect it resembles nitrous oxide gas. Its effects ar stronger than nitrous oxide and the anaesthesia is suffi ciently deep to be employed for operations requiring mus cular relaxation but this relaxation is less than ether.

The gas as obtained in compressed cylinders has garlic smell and although the patient does not perceive for more than a few breaths, it is annoying to the anaes thetist and other occupants of the room.

The usual practice is to give 90 p. c. of the gas wit 10 p. c. of oxygen. For prolonged use it should be mor freely diluted with 20 p. c. oxygen. As a rule the perio of excitement is absent or relatively slight and the resp ration is not affected, but remains slow and regular. Th medullary centres are stimulated slightly by the lowere oxygen concentration. The skin remains dry and ther is no perceptible increase either of perspiration or of sal vary secretion.

Recovery takes place quickly, within two to three minutes, after withdrawal of the anaesthetic.

It is used in the same way and with the same apparatus as nitrous oxide ; it is however safer, asphyxia or cyanosis being absent. As compared to nitrous oxide gas it produces complete muscular relaxation and deeper anaesthesia. Moreover excitement is less and recovery is more quick. In addition to its use in surgical practice it may be of special value in obstetric practice as it does not inhibit uterine contraction during labour.

It differs from ether in being more pleasant, prompt and safe. There is absence of gas pains and vomiting, renal and pulmonary complications.

Caution.—The gas is inflammable and when mixed in certain proportions with air or oxygen it becomes explosive. Ethylene and nitrous oxide mixture is highly explosive. It should not be used where flame or cautery is used.

NITROGENII MONOXIDUM. (Nitrogen. Monox.). N_2O. Syn.—Laughing Gas.—Nitrous Oxide is supplied compressed in metal cylinders. Contains not less than 95 p.c. v/v of nitrous oxide.

Characters.—A colourless gas, heavier than air, with a characteristic odour and faint sweetish taste.

Pharmacology and Therapeutics

Nitrous oxide is a gas and produces **general anaesthesia** almost instantaneously, partly by direct narcotic action on the central nervous system and partly by exclusion of oxygen. Its action on the central nervous system is possibly due to its solubility in lipoids. The mixture used contains 20 p.c. of air and so 4 p.c. of oxygen, therefore the inhalation cannot be continued for more than a few minutes. Nevertheless it produces sufficient anaesthesia to enable the surgeon to perform small operations, like extraction of tooth or incision of an abscess, painlessly.

The anaesthesia is brought about so quickly that the different stages can hardly be differentiated. At the beginning there is some buzzing of the ear and indistinctness of vision, soon followed by impairment of consciousness, a pleasurable sensation, and a tendency to laugh (hence the name laughing gas). As soon as the inhalation is stopped the patient returns to consciousness, and the cyanosis disappears within half to quarter of a minute The pulse becomes slower and fuller, and the respiration returns to normal.

For prolonged anaesthesia the gas is used with oxygen, to prevent too high a degree of cyanosis. For this a special apparatus is necessary so that the gases may be mixed to any proportion. The inhalation is started with pure nitrous oxide for a few seconds and then oxygen is admitted and slowly increased until cyanosis disappears, which

occurs usually with 90 per cent. of nitrous oxide and 10 per cent. of oxygen. Sometimes it is given after a preliminary dose of morphine and hyoscine. When given with oxygen there is less disturbance of the vital centres than with any other general anaesthetic. Moreover, the anaesthesia can be prolonged without any fall of blood pressure, depression of respiration or post-operative shock.

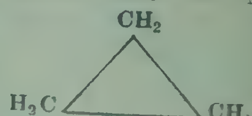
It is impossible to obtain with nitrous oxide and oxygen alone sufficient muscular relaxation, because at the ordinary atmospheric pressure the blood cannot take up sufficient nitrous oxide to produce deep anaesthesia. If, however, it is used with small quantities of ether, a relaxation of the muscle is obtained which is out of proportion to the amount of ether used, and this becomes more marked when ether and chloroform are used in combination. To secure better control of the proportion of gas and oxygen various forms of apparatus have been devised. For small operations it is administered through a tight-fitting mask to exclude air.

Gas and oxygen is the ideal anaesthetic because of its nearest approach to 100 per cent. safety. Unfortunately the apparatus used is expensive and bulky and is liable to mechanical breakdown and requires constant and careful looking after to keep it in working order.

As a rule no after-effects are observed, and it is practically devoid of any danger except asphyxia from want of oxygen which may cause a rise of blood pressure to a dangerous extent in elderly persons. Some complain of giddiness, headache and drowsiness.

Contraindications.—Undiluted or high concentration is contraindicated in patients to whom asphyxia even for a brief period would be harmful, especially in elderly persons with arteriosclerosis. It is almost impossible to anaesthetise hysterical and highly excited persons. It is also contraindicated in those suffering from valvular and myocardial disease, obese and anaemic persons, and in operations on the brain.

CYCLOPROPANE. (Cycloprop.).—Cyclopropane may be prepared by the action of zinc on 1 : 3-dibromopropane. Contains not less than 99 p.c. v/v of C_3H_6. For convenience in use it is compressed in metal cylinders.



Characters.—A colourless gas at atmospheric temperature and pressure ; inflammable ; mixtures with oxygen and air at certain concentrations are explosive ; odour characteristic. One volume dissolves in about 2.7 volumes of water at 15°C. Very *Soluble* in alcohol (90 p.c.), in solvent ether and in chloroform.

Pharmacology and Therapeutics

Cyclopropane or trimethylene is a gas and an isomer of propylene, heavier than air and inflammable. It is a powerful anaesthetic with a high degree of lipoid solubility

though less than ether and chloroform and will produce narcosis in low concentrations (4 p.c.) and may be used mixed with air or oxygen. Ten p.c. cyclopropane in oxygen is sufficient to produce light anaesthesia ; 15 to 20 p.c. with 85 to 80 p.c. of oxygen produces muscular relaxation. If the concentration is increased or after prolonged administration of even a weak mixture, cardiac arrhythmias may arise.

It is a safe, pleasant, non-toxic anaesthetic producing relaxation of muscles. Its action is more rapid than ether, but less so than nitrous oxide or ethylene. Since it does not irritate the respiratory tract, no respiratory irregularities are noticed. For the same reason salivation is not prominent. Although a gas its anaesthetic potency is like chloroform, and the anaesthetist should not rush the patient from one stage to another. The anaesthesia can be maintained for several hours if required.

Recovery occurs within a few minutes after cessation of the anaesthesia as quickly as from nitrous oxide or ethylene. Nausea and vomiting are less common.

Since the gas is non-irritating, any signs of sudden increase of concentration of the anaesthetic as manifested by coughing, apnoea, laryngospasm, or struggling are not observed. As it does not stimulate respiration, its use is not followed by any initial increase of respiratory rate observed with ether, nitrous oxide or ethylene. Changes in the rate of the pulse should give warning to the anaesthetist ; slowing of the rate to 50 or even less or a definite tachycardia are *danger signals* for decreasing the concentration of cyclopropane.

It is administered in closed circuit apparatus with carbon dioxide absorption technique with oxygen.

Cyclopropane may be used as an anaesthetic in all surgical operations, but it is of special value where maintenance of tissue oxygen is of great importance, as in patients suffering from Basedow's disease, in pregnancy, anaemia, and bad risk cardiac cases, *e.g.* total thyroidectomy for congestive heart failure. It is of special value in chest surgery where a quiet respiration, absence of bronchial irritation or spasm of the larynx, plenty of oxygen and quick recovery are so very essential for the success of the operation.

Advantages.—High percentage of oxygen with full anaesthesia without premedication, and absence of irritation of respiratory passages ; wide margin of safety between the anaesthetic and toxic concentrations, which is 13 p.c. against 43 p.c., more than that existing for any other anaesthetic now in use. There is absence of any deleterious metabolic effects ; no depressant effect on the heart or circulation in anaesthetic concentrations ; rapid elimination.

Disadvantages.—Possibility of explosion. It is however less explosive than ethylene, or nitrous oxide and ether mixture, but care is necessary if cautery or electric knife is used, when no gas

should be released from the breathing bag. Chances of haemorrhage from dilatation of the peripheral vessels which may increase capillary oozing ; tendency to respiratory depression or even arrest during deep anaesthesia. Since oxygen is given in excess there is absence of any change of colour of the skin which remains pink at all times.

Premedication and Basal Anaesthesia

As a supplementary to pre-operative preparation, it is often advisable to give the patient in the evening before the operation some mild sedative or hypnotic so as to ensure good rest at night which may otherwise be prevented. This conserves the patient's strength against postoperative fatigue and weariness which may follow the administration of an anaesthetic and the operative procedure. The administration of a hypnotic must be done with due regard to the premedication proper which is administered prior to operation, i.e. to produce *basal narcosis*, which means a state of unconsciousness produced by a non-volatile substance which serves as a base upon which complete anaesthesia can be built by the administration of a volatile anaesthetic. Attempts are now being made to use some non-volatile narcotics as adjuvant drugs before the administration of the anaesthetic proper, with the object of protecting the nervous system by producing profound sleep, thus making the patient indifferent to subsequent happenings. In fact this method is receiving considerable importance, and more reliance is being placed on these preliminary measures than on the subsequent anaesthetic. It obviates all nervous apprehensions and mental distress so often responsible for true shock, and is of great value in nervous patients, those suffering from hyperthyroidism and in children. This method while retaining the advantages of volatile anaesthetics minimises the difficulties incidental to the induction of anaesthesia.

Apart from relieving the patient from pre-operative anxiety, the post-operative pain is also avoided as the patient sleeps for several hours afterwards. Basal narcosis also reduces considerably the amount of volatile anaesthetics.

Unfortunately the prolonged post-operative sleep may lead to pulmonary complications resulting from respiratory depression. It is therefore essential that preparations which are rapidly excreted or detoxicated with short duration of action should be used in combination anaesthesia. In any case no other narcotic should be used after operation until the patient becomes completely conscious and complains of pain or is very restless.

The drugs used for the purpose are :—

Hyoscine Hydrobromide 1/200 gr. or **Atropine Sulphate** 1/100 to 1/60 gr. and **Morphine Hydrochloride** 1/6 gr. administered an hour

before the anaesthetic is given. Atropine is preferred to hyoscine as it does not depress the respiration and prevents reflex vagus inhibition of the heart.

Paraldehyde, administered per rectum in doses of 60 ms. for every stone of body weight, diluted with glucose saline.

Bromethol, also administered per rectum in 2.5 p.c. solution in distilled water.

Hexobarbitone Sodium.—When used intravenously it produces rapidly deep anaesthesia of short duration, since it is rapidly detoxicated by the liver and the portion remaining unchanged being excreted in the urine. It is therefore largely used in minor surgery where the operation does not extend more than twenty to thirty minutes and where much muscular relaxation is not required. As a basal anaesthetic it is valuable, full anaesthesia being maintained by the use of some volatile anaesthetic like ether. The usual dose is 2 to 3 mils of a 10 p.c. solution in sterile distilled water. The injection is given with the patient lying down at a rate of 1 mil in 15 seconds. For short operations the same amount is further added, and twice as much for long operations. For elderly and debilitated patients half the amount required to produce sleep should be given. It may be administered per rectum after a soap-water enema. The dose is 3 ms. of the 10 p.c. solution per pound of body weight.

The chief danger is respiratory depression and fall of blood pressure. It should not therefore be used in patients suffering from affections of the respiratory tract and low blood pressure, and also in those who are suffering from impaired liver function.

A deep yawn just before the disappearance of consciousness, twitching of the face muscles and jactation of the limbs are common. Pupils are moderately dilated and react to light. Corneal reflex is lost during complete anaesthesia. The patient regains consciousness in ten to twenty minutes, but remains drowsy and drops off to sleep again if left undisturbed.

Pernocton.—Sodium beta-bromallyl- barbituric acid. This is given intravenously about quarter of an hour before starting the inhalation anaesthesia. Resembles nembutal, but it is a more powerful hypnotic and less safe. The dose is 1 mil of a 10 p. c. solution per 12.5 kilo of body weight *intravenously*, may also be given *intramuscularly*. Does not produce any marked fall of blood pressure like amytal. No morphine is required but atropine may be given with advantage.

Luminal is given by the mouth on the evening before operation, 10 grs. at 9 p.m. If the patient is drowsy in the morning, half the dose is given two hours before operation.

Pentobarbitone Sodium or **Nembutal** is more sedative than hypnotic, and is less often followed by restlessness or delirium and is safer than amytal. It closely resembles amytal and produces sleep in smaller doses but more quickly. The sleep is of shorter duration due possibly to its rapid destruction in the liver. For production of basal narcosis it is given intravenously ten minutes before operation. The solution should be freshly prepared and must be quite clear, and the injection given with the patient in bed, or on the operation table with a solution of 7½ grs. (0.5 grm.) in 10 mils at the rate of 1 mil per minute ; the dose being the minimum amount required to put the patient into a quiet sleep. It may be given by *mouth* or *per rectum*, about one to two hours before operation. Usually one injection of atropine 1/100 gr. and morphine 1/8 gr. is given half an hour before.

Thiopentone Sodium or **Pentothal Sodium** is used as a basal anaesthetic intravenously. Its use should be supplemented by gas-oxygen anaesthesia with excess of oxygen. The solution used should

be $2\frac{1}{2}$ p.c. instead of 5 p.c. as ordinarily recommended and injection given very slowly. As it is a sclerosing fluid 5 p.c. solution may produce thrombosis. If introduced into an artery it produces immediate burning sensation in the limb distal to the point of injection, when further injection should be stopped and the needle withdrawn immediately. Special care should be taken for those cases who received either repeated or single high doses of morphine. While giving injection watch the patient for developing unconsciousness and continued respiration; watch the syringe to see how much of the solution is being injected. Always keep the air way clear. Ordinarily no fixed dose is necessary, the amount that each patient needs is determined by his reaction to the drug as it is administered. Generally the patient requires a total of twice the sleep dose. Put the patient in a stable position, so that when he relaxes he may not slump into a new position.

Sodium Amytal (sodium iso-amyl-ethyl-barbiturate) is a powerful hypnotic and rapidly produces loss of consciousness and general anaesthesia. It is given intravenously in 10 p.c. solution at the rate of 1 mil per minute. Unconsciousness is induced very rapidly, and lasts for four to six hours or more and the patient remains drowsy for about a day. The usual quantity required being 7 to 15 grs. It reduces the amount of ether by ten per cent. As the anaesthesia is produced very rapidly the injection is given a few minutes before operation. Owing to its effect on respiration and vaso-motor centre, it causes a great fall of blood pressure and respiratory weakness. It is however completely destroyed in the system.

Soneryl Sodium.—Sodium derivative of butylethyl-barbituric acid. A sedative and hypnotic. Administered as a pre-anaesthetic basal narcotic in doses of $2\frac{1}{4}$ grs. per 36 pounds body weight. It is closely allied to nembutal but less toxic and has the advantage of being effective when given orally an hour before operation and atropine half an hour later. The sleep after operation is not excessive, but some patients become restless which is easily controlled by morphine. Except some depression of breathing in a few instances no other complication has been recorded.

Contra-indications of basal intravenous anaesthesia :—

1. Those having any respiratory obstruction or dyspnoea and in operations of the air passages.
2. Those whose liver is either diseased or there is impairment of its function. It is better avoided in those who are suffering from chronic kidney disease.
3. Children, because of the difficulty in giving intravenous injection and because of the small air way.
4. Those suffering from myocarditis, high blood pressure or low blood pressure.

3. Hypnotics and Analgesics

Hypnotics are drugs or measures employed to induce or maintain sleep. Sleep is a natural phenomenon which comes on spontaneously when the reflex activity of the central nervous system is inhibited to a degree which is usually accompanied by unconsciousness. The unconsciousness is not deep, as in coma, but more or less shallow. Like most habits, sleep is to a certain extent under voluntary control, and is a natural sequence which follows after a period of wakefulness. Prolonged sleeplessness is accompanied by various pathological changes in the cerebral cortex and the appearance of some toxin in the blood.

A proper use of hypnotics implies a knowledge of the mechanism of sleep and the different factors concerned in producing sleeplessness or insomnia. As long as the mechanism of sleep remains in part unexplained the treatment of insomnia must at best be empirical. Sampson Wright has put forward the theory that it may be due to the damping down of the conductivity in the afferent and association paths in the nervous system. Although such a conception does not explain all the factors concerned in sleep, it acts as a reminder to the physician of the existence of the paths through which sleeplessness may come. Besides there are extro-ceptive impulses from the external surroundings of the patient through the surface of the body and special senses ; the proprio-ceptive impulses from the posture of or pressure on the muscles, bones, joints and from the large group of visceral stimuli, of which the cardio-vascular, gastric and rectal are the most important.* The fact remains however that accompanying sleep there is a depressed activity of the cerebral cortex, and that any factor, physical or mental, which tend to perpetuate cortical activity—pain and dyspnoea, worry and strain—render sleep more difficult.

An intimate relation exists between sleep, hypothalamus and the autonomic nervous system. Sleep is regulated by centres in the hypothalamus and lesions in this region, as happens in encephalitis lethargica, are associated with disturbance in the sleep regulating mechanism producing either prolonged sleep or marked sleeplessness. During sleep the parasympathetic activity is increased as is evidenced by slow pulse, constriction of the pupils, constriction of the bronchi, while the digestive juices and gut movements remain active. Further, it has been shown by Hess that injection of ergotamine into the third ventricle, and by Dikshit that intraventricular injection of acetylcholine, produced sleep.

Whatever may be the underlying factors in the production of natural sleep, it is evident that in the majority of cases of insomnia the cause is the presence of some factors inimical to that state of physical or mental equanimity so essential to natural sleep, and the rational course of treatment would be to remove the disturbing factor.

The following factors are mostly responsible for sleeplessness :—

I. **Obstructive.**—1. *Pain*, from whatever cause it may arise, and the proper treatment is to allay the pain either by dealing directly with the primary disease responsible for it, or to make the patient forget its presence by the use of such drugs as morphine or any of its allies, bar-

**Practitioner*, *Feb.*,1938. Ibid. *Sept.*, 1936.

biturates or other analgesics according to the intensity of the case.

2. *Certain general and visceral diseases.*—Diseases of the heart, vessels, kidneys, etc., often cause sleeplessness. Cough and dyspnoea are often responsible for sleeplessness. Cough may be a part of serious lung complication, or due to some local trouble in the throat. The rational treatment is to remove the disturbing factor, whenever possible, supplemented by the use of proper hypnotic drugs. Digitalis will often induce sleep in dyspnoea from failure of the heart.

3. *Intoxications.*—Excessive tea and coffee drinking often cause insomnia. With some people a cup of tea or coffee before bedtime will cause sleeplessness.

4. *Infectious diseases*, when accompanied by high fever, *e.g.* malaria, pneumonia, etc.

5. *Diseases of the Brain.*—(*a*) Organic, as tumour, meningitis, syphilis ; and (*b*) mental, as mania, delirium tremens, etc.

II. Psychoneurosis.—By far the largest number of insomnia comes under this head which plays an important part in the mental and emotional excitement. These may be worry, grief, neurasthenia, hysteria, hypochondria, etc. A state of anxiety or preoccupation is a common factor in the production of insomina, for instance, the dread of not being able to sleep, active mental work, exciting companions, disturbing surroundings, etc., before sleep. Often times the patient goes to bed with his mind fixed on the necessity of sleep—a state specially liable to perpetuate sleeplessness.

According to Verworn sleep is due to (1) lessened irritability, *i.e.* fatigue of the cells of the cerebral cortex which results from work ; (2) removal of external stimuli, as noise, light, etc. A sound which is of a monotonous nature, *e.g.* continuous falling of rain, or a mild form of peripheral stimulus, which will not excite any emotion, will have a soothing effect on the brain cell conducive to sleep. Many cases of insomnia due to psychoneurosis yield to suggestion. If the patient knows that he will get something for sleep, the knowledge will of itself bring on sleep. At the same time if he knows that the drug is to be discontinued or the dose reduced, the dread of a sleepless night will cause insomnia. Similarly if an injection of, say, morphine is given to produce sleep, oftentimes an injection of some inert substance, even water, will have the same mental effect to produce sleep. The effect of monotonous sound,

monotonous thought and monotonous sight in the production of sleep is well depicted by Wordsworth.*

The different hypnotics vary in their speed of action, duration of their effect and suitability for various ages and physical states. It is useless for instance to order a hypnotic when the patient is up and about, or to prescribe paraldehyde to a patient who goes to sleep in time but wakes up after 3 to 4 hours.

The action of hypnotics resembles somewhat that of general anaesthetics but is slower in its onset, less powerful, more lasting and is not intended to produce a deep stage of narcosis. An ideal hypnotic must not irritate the stomach and should be absorbed readily, so that sleep may be induced at a regular interval after its administration and without producing any preliminary excitement. It should not be volatile and must not be excreted too rapidly by the lungs. It should not produce any narcotic effect, *i.e.* should not depress the cerebrum more than the sleep stage, and should have no untoward effect either on the vital medullary centres, or the heart. There must be a sufficient margin of safety between the therapeutic and toxic doses. Moreover, it should not have any toxic effect even when used for a prolonged period and should not form a habit. Such an ideal hypnotic is not known at present.

Of the different hypnotics, chloral, bromides, paraldehyde, bromethol act by *depressing the cerebral cortex* ; while the barbituric acid group act by *depressing the thalamic region.* The barbiturates therefore, in addition to the hypnotic effect, are markedly sedative and are of great service in conditions characterised by motor hyperexcitability. Morphine and hyoscine are supposed to act on both the regions.

Analgesics are drugs which relieve pain without loss of consciousness. General anaesthetics also abolish pain but this is produced when the patient becomes unconscious and are not classed as analgesics. Other drugs again relieve pain without any direct analgesic action. To this class belongs spasmolytic drugs. Thus, amyl nitrite will prevent or abolish anginal pain because of its vaso-dilator effect. The drugs of the antipyretic group, namely, antipyrin, phenacetin, etc., are analgesics and are known as "coal tar analgesics". To this group also belong the salicylates and aspirin. These will be described under antipyretics. Morphine and its derivatives are hypnotics

*"A flock of sheep that leisurely pass by,
One after one ; the sound of rain, and bees
Murmuring ; the fall of rivers, winds and seas,
Smooth fields, white sheets of water, and pure sky ;
I have thought of all by turns, and yet do lie
Sleepless !"

and analgesics. It is presumed that these analgesics act by forming some sort of barrier and prevent nerve impulses carrying pain sensation to reach consciousness and the site of action may be cerebral cortex or the thalamus. Because of their liability to produce addiction and other side-effects attempts are being made to replace these drugs by newer synthetic compounds, e.g., pethidine and amidone.

Analgesics are classified as (a) local ; and (b) central.

(*a*) *Local analgesics.*—These abolish pain sensation in a specified area by acting on the peripheral sensory nerves ; they are :—Cocaine and its derivatives, cinchocaine, ethyl chloride spray, freezing, quinine urethane. Phenol, menthol, hydrocyanic acid, belladonna, aconite, chlorbutol also produce certain amount of local analgesia.

(*b*) *Central analgesics.*—Morphine and its derivatives, pethidine, amidone, coal-tar analgesics (antipyretic group), salicylates, aspirin, cinchophen and to a less extent barbiturates and cannabis indica.

Hypnotics may be classified as follows :—

A. **Organic :—**

1. Analgesic Hypnotics

Opium, Morphine, Codeine, Pethidine Hydrochloride, Amidone, Hyoscine. Opium, Morphine and its derivatives produce sleep and relieve pain. **Pethidine and Amidone** are more analgesic than hypnotic.

2. Aliphatic Hypnotics
   - (*a*) Chloral Group : **Chloral Hydrate, Butyl-chloral Hydrate, Chlorbutol, Chloralformamide.**
   - (*b*) Aldehyde and Alcohol Group : **Paraldehyde, Amylene Hydrate, Bromethol**
   - (*c*) Sulphonal Group : **Sulphonal, Methylsulphonal.**
   - (*d*) Urea Derivatives : **Barbitone, Soluble Barbitone, Phenobarbitone, Soluble Phenobarbitone, Hexobarbitone, Soluble Hexobarbitone, Methylphenobarbitone, Pentobarbitone Sodium, Soluble Thiopentone, Phenytoin Sodium, Urethane.**

Paraldehyde, Bromethol and some of the Barbiturates are also used as sedatives and anaesthetics.

3. Aromatic Hypnotics
   - (*a*) Alkaloidal Hypnotics : **Opium, Morphine, Codeine, Diamorphine, Hyoscine.**
   - (*b*) **Phenacetin, Acetanilide, Amidopyrine, Phenazone, Acid Acetylsalicylic. These are not true hypnotics but often produce sleep by relieving neuralgic pain through their analgesic action.**

B. Inorganic : **Potassium Bromide, Sodium Bromide, Ammonium Bromide.**

These diminish hypersensibility of the nervous system so that pain is less keenly felt.

1. Analgesic Hypnotics

OPIUM

Syn. I. V.—*Afim*, Beng., Hind. *Ahifen*, Sans.

Source.—Opium is obtained by incision from the unripe capsules of *Papaver somniferum*, dried or partly dried by heat or spontaneous evaporation. It contains in its moist condition, not less than 9.5 p.c. of morphine.

Characters.—More or less rounded, usually somewhat flattened masses, varying in weight, from 250 and 1000 grammes ; covered with portions of poppy leaves, and usually with fruits of species of *Rumex* adhering to the masses. When fresh, plastic, becomes hard and tough on keeping, or brittle. Odour, strong and characteristic. Taste, bitter.

Varieties.—(*a*) *Turkey opium*, produced in Asia Minor, in rounded, irregular or flattened masses, usually enveloped in poppy leaves or fruits of a species of *Rumex* to prevent the masses from adhering to one another. Two varieties, viz. "Soft Shipping," which may contain up to 30 p.c. of moisture, and the "Druggists opium" which contains less moisture and less per cent. morphine. (*b*) *European opium*, chiefly produced in Belgium, Greece and Yugoslavia, is of a higher quality than the "Soft Shipping" variety of Turkey opium which it resembles in general characters. (*c*) *Persian opium* in brick shaped masses weighing about 1 lb. It contains less moisture, is homogeneous in character, and usually contains varying proportions of native gum to give the consistence suitable for moulding them into bricks. (*d*) *Indian opium*, occurs in two forms, viz., *Abkari* or *excise opium* in square cakes covered with Nepal paper ; *Medicinal opium*, in cakes and powder.

Composition.—The important alkaloids belong to two groups (1) *pyridine-phenanthrene*, represented by morphine, codeine and thebaine; and (2) *benzene-isoquinoline*, represented by narcotine, papaverine, laudanosine, narceine, hydrocotarnine, etc.

(1) *Primary alkaloids*, 18 in number which form a closely related series at one end of which stands *morphine*, with its dominant property, the narcotic one, and at the other end *thebaine* with a typical strychnine action on the cord. On account of these other substances opium is less narcotic than morphine :—*Morphine* about [illegible] to 21 p.c. ; *Codeine* about 0.3 to 0.8 ; Thebaine about 0.3 p.c. ; Anarcotine or Narcotine 2 to 7 p.c. ; Narceine, Papaverine, Pseudo-morphine, Cryptopine, Protopine, Hydrocotarnine, Laudanine, Laudanosine, Meconidine, Rhoeadine, Codamine Gnoscopine, Lanthopine, Xanthaline.

(2) *Secondary Alkaloids or Derivatives*, 8 in number :—Apomorphine, Oxydimorphine, Apocodeine, Desoxycodeine, Thebenine, Porphyroxine, Cotarnine, Rhoeadinine.

(3) *Indifferent Substances*, 3 in number :—Opionin, Meconin, Meconoidin.

(4) *Organic Acids*, 2 in number :—Lactic acid, Meconic acid. (5) *Water.*—About [illegible] p.c. **(6) Resin, glucose, fats, caoutchouc, essential oil.** odorous substances and salts of ammonium, calcium and magnesium.

Variation in composition.—The percentage of morphine varies in Patna opium from 3 to 5, and in Smyrna opium from 5 to 10.5, whereas that of narcotine in the former 4 to 6 and in the latter 1 to 2.

Opium Pulveratum. (Opium Pulverat.).—Powdered Opium. **Syn.**—Pulvis Opii.—Opium dried and reduced to a fine or moderately fine powder, and adjusted if necessary, by the addition of powdered lactose to contain 10 p.c. of morphine, or 3/10 gr. morphine in 3 grs.

Characters.—A light brown powder, consisting of yellowish-brown or brownish-red particles ; odour and taste, of opium.

B. P. Dose.—1/2 to 3 grs. or 30 to 200 mg.

Official Preparations

1. **Pulvis Cretae Aromaticus cum Opio.**—Contains 0.25 p.c. of morphine ; or 1/7 gr. morphine in 60 grs. or 2.5 p.c. of powdered opium. **B. P. Dose.—10 to 60 grs. or 0.6 to 4 grms.**

2. **Pulvis Ipecacuanhae et Opii.** *Syn.—Pulvis Ipecacuanhae Co ; Dover's Powder.*—10 p.c. of opium or 1 p.c. morphine or 1/10 gr. morphine in 10 grs. **B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.**
   - (*a*) **Tabellae Acidi Acetylsalicylici cum Ipecacuanha et Opio.** *Syn.—Tablets of Aspirin and Dover's Powder.*—Contains 2½ gr. of each. **B. P. Dose.—1 to 2 tablets.**
   - (*b*) **Tabellae Ipecacuanhae et Opii.** *Syn.—Dover's Powder Tablets.*—**B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.** *N. B.*—**If the quantity in each tablet is not mentioned, 5 gr. tablet should be supplied.**

3. **Tinctura Opii.** *Syn.—Laudanum.*—Contains 1 p.c. morphine, or 1/3 gr. in 30 ms. **B. P. Dose.—5 to 30 ms. or 0.3 to 2 mils.**

4. **Tinctura Opii Camphorata.** *Syn.—Tinct. Camphorae Co. ; Paregoric ; Paregoric Elixir.*—0.05 p.c. w/v morphine, or 1/30 gr. in 60 ms. **B. P. Dose.—30 to 60 ms. or 2 to 4 mils.**

Non-official Preparations

1. **Suppositorium Plumbi cum Opio, B.P.C.—Lead acetate 3 grs. and powdered opium 1 gr. in each.**

2. **Pilulae Plumbi cum Opio, B. P. C.—Lead acetate $1^{3}/_{5}$ grs. and opium about 1/4 gr.** for each pill with syrup of glucose. *Dose.*—1 to 2 pills.

3. **Unguentum Gallae cum Opio, B.P.C.**—Ointment of gall and opium. Opium 7½ p.c.

4. **Liquor Opii Sedativus, B.P.C.—Contains 3/10 gr. morphine. in 30 ms. Dose.—5 to 30 ms. or 0.3 to 2 mils.**

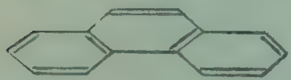
5. **Pilulae Hydrargyri cum Creta et Opii, B. P. C.**—*Syn.—Hutchinson's Pills.*—Grey Powder and Dover's powder, each 1 gr. for each pill. *Dose.*—One pill.

6. **Narcotina.** *Syn.—Anarcotine.*—White inodorous crystalline prisms. Insoluble in water. It is not a hypnotic but is an antiperiodic. *Dose.*—1 to 3 grs. or 0.06 to 0.2 grm.

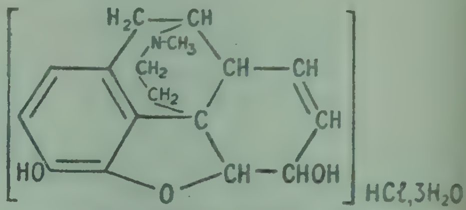
7. **Cotarnine Chloride.** *Syn.—Stypticin.*—The chloride of an alkaloid prepared from narcotine. Yellow crystalline powder ; very soluble in water and alcohol. Useful in *uterine haemorrhage*, and to check bleeding from the urethra after catheterisation. **Dose.—1/3 to 1½ grs. or 20 to 100 mg.**

8. **Papaveretum, B.P.C.** *Syn.—Omnopon ; Pantopon.*—Consists of the hydrochlorides of alkaloids of opium. Contains 50 p.c. of anhydrous morphine and 50 p.c. hydrochlorides of the remaining alkaloidal constituents of opium. Soluble brown powder. Used for the same purposes as opium. Usually used hypodermically. A [illegible] p.c. solution in a mixture of 3 parts of water and 1 part of glycerin is suitable for internal administration or hypodermic use. The preparations for injection may be sterilised by heating. **Dose.—1/6 to 1/3 gr. or 10 to 20 mg. by mouth : 1/12 to** 1/6 gr. or 5 to 10 mg. by injection.

MORPHINAE HYDROCHLORIDUM. (Morph. Hydrochlor.). $C_{17}H_{19}O_3N,HCl,3H_2O$.—Morphine Hydrochloride is the hydrochloride of an alkaloid, morphine, obtained from opium.



Phenanthrene nucleus



Morphine Hydrochloride

Characters.—Colourless glistening needles or crystalline powder; odourless; taste, bitter. *Soluble* in 25 parts of water, 50 parts of alcohol (90 p.c.), insoluble in solvent ether and chloroform. Aqueous solution neutral to litmus.

B. P. Dose.—1/8 to 1/3 gr. or **8 to 20 mg.**

Official Preparations

1. **Liquor Morphinae Hydrochloridi.**—Contains 1 p.c. w/v of morphine hydrochloride, or 1/4 gr. in 30 ms. **B. P. Dose.—5 to 30 ms. or 0.3 to 2 mils.**
2. **Suppositoria Morphinae.**—Contains 1/4 gr. morphine in each.
3. **Trochiscus Morphinae et Ipecacuanhae.**—1/32 gr. morphine and 1/10 gr. ipecacuanha in each.

Morphinae Sulphas. (Morph. Sulph.). $(C_{17}H_{19}O_3N)_2, H_2SO_4, 5H_2O$. —Sulphate of an alkaloid, morphine, obtained from opium.

Characters.—White acicular crystals or cubical masses, or a white crystalline powder; odourless; taste, bitter. *Soluble* in 24 parts of water, in 700 parts of alcohol (95 p. c.); insoluble in solvent ether, and in chloroform.

B. P. Dose.—1/8 to 1/3 gr. or **8 to 20 mg.**

Official Preparations

1. **Injectio Morphinae Sulphatis.—B. P. Dose.—1/8 to 1/3 gr. or 8 to 20 mg.**
2. **Injectio Morphinae et Atropinae.**—Contains 1/100 gr. atropine sulph. and 1/6 gr. morph. sulph. in 15 ms. **B. P. Dose.—8 to 15 ms.** or **0.5 to 1 mil.** *subcutaneously.*

Non-official Preparations

1. **Linctus Morphine, U. C. H.**—Liq. Morph. Hydrochlor. 3 ms., Chloroform emulsion 3 ms., Treacle 60 grs., Water to 1 dr. *Dose.*—1 dr. three or four times or oftener daily. Children of 8 to 14 years, 10 to 20 drops.
2. **Tinctura Chloroformi et Morphinae Co., B.P.C.**—Chloroform 3/4 m., Acid. Hydrocyanicum Dil. 1/2 m., and Morphine Hydrochlor. 1/11 gr. in 10 ms. *Dose.*—5 to 15 ms. or 0.3 to 1 mil.
3. **Dionin.** *Syn.—Ethylmorphine Hydrochloride U.S.P.*—White or yellowish crystalline powder, soluble in water. Pleasant substitute for morphine without its undesirable effects. Recommended in morphine habit. It has properties intermediate between morphine and codeine, but does not depress respiration to the same extent as morphine. Relieves dry *hacking cough.* Useful in *bronchitis* and *whooping cough.* A useful anodyne in *glaucoma, iritis, corneal ulcers,* etc., when used locally. *Dose.*—1/4 gr. or 15 mg.
4. **Dihydromorphinone Hydrochloride, B.P.C.** *Syn.—Dilaudid.*—Colourless, bitter crystals, freely soluble in alcohol and water. 1/32 gr. is equivalent to 1/6 gr. morphine as an analgesic. Used in place of morphine. Affects respiratory centre like morphine. Does not cause severe constipation and is less liable to form habit. May cause transient nausea and giddiness. *Dose.*—1/24 to 1/12 gr. or 2.5 to 5 mg.; 1/30 gr. or 2 mg. *subcutaneously.*
5. **Eukodal.**—Hydrochloride of dihydroxycodeinone. Prepared from thebaine. White crystalline powder, soluble in water. Not so toxic as dilaudid or dicodid and does not cause convulsion. It has much weaker action on the intestinal movements than the other two. It is more depressant to the respiratory centre than morphine. A substitute for morphine as an analgesic and sedative. Depresses the vagal centre. Used in all cases where morphine is indicated. Does not produce vomiting or constipation. Though prepared from non-habit forming drug it is liable to produce a habit. *Dose.*—As analgesic, 1/12 to 1/6 gr. (5 to 10 mg.) or 1 to 2 tablets; 1/6 to 1/3 gr. (10 to 20 mg.) subcutaneously.

Pharmacology of Opium and Morphine

Externally.—Opium and its alkaloids have no action on the sensory nerve endings or on the peripheral nerves. As morphine is absorbed to a slight extent from the un-

broken skin and freely from the mucous membrane there may be some central analgesia.

Internally. **Mouth and stomach.**—In moderate doses opium causes dryness of the mouth, tongue and throat from **diminished secretion** due to its depressant action on the secretory centre of the salivary and the mucus glands after absorption. In the stomach small doses ($\frac{1}{12}$ gr.) diminish the sensation of hunger and slightly increase its movements ; but larger doses cause **contraction of the pyloric sphincter and relaxation of the fundus,** and retards the passage of its contents by several hours. The gastric movements are diminished, the secretion is reduced, and pain is relieved. Opium therefore relieves pain, lessens appetite and retards digestion. These effects are central and observed after the drug is absorbed. It often causes nausea and vomiting which are not due to irritation of the gastric nerves, since they are not so marked in the early stage, but occurs during recovery from its effects and even when used subcutaneously, and is due to stimulation of the vomiting centre ; the centre is depressed in large doses.

Intestine.—In the intestine opium **reduces secretion, relieves pain** and **produces constipation.** The cause of constipation has been differently explained by different observers. While some demonstrated diminished peristalsis, others claimed marked stimulation. Apart from individual variations, it is possible that the presence of other alkaloids, specially papaverine and narcotine, which have a strong depressant action on peristalsis, may be responsible for the difference in the effects produced. The chief action of morphine in the small intestine is **increased motor** activity (tonus) and **decreased propulsion** (peristalsis). In the colon it causes increased and prolonged contraction of the circular muscles causing tonic rings and diminish or even abolish propulsive waves. These effects suppress the normal peristaltic waves and retard the passage of the contents downwards. The spasm of the ileo-caecal and anal sphincters together with the tonic contraction of the pyloric sphincter, already referred to, allow the food materials to remain for a longer time, thus helping more complete absorption of fluids and accumulation of inspissated faecal mass. Moreover, owing to the central effect, the rectal sensation is diminished and the defaecation reflex becomes sluggish. Opium therefore is a **sedative, astringent** and **anodyne** to the bowels. It also relieves, through central effect, pain and irregular peristalsis.

The different factors concerned in producing constipation are :—(1) delay in emptying the stomach owing to pyloric spasm and relaxation of the stomach wall ; (2) diminished reflex peristalsis owing to loss of sensation ; (3) spasm of ileo-caecal and anal sphincters ; (4)

spastic contraction of the colon ; (5) diminished secretion of pancreas and bile which decrease digestive process in the small intestine ; and (6) sluggish rectal sensation and defaecation reflex.

The mechanism of the gastro-intestinal effects is not clear. It has been suggested that the action may be cholinergic since denervation and administration of neostigmine enhance its action and that atropine will counteract the gastro-intestinal effects. It should be noted that opium is superior to morphine in relieving intestinal pain and producing constipation, due firstly to its slow absorption, and secondly to the presence of isoquinoline derivatives, *viz.*, papaverine and narcotine which induce relaxation of the plain muscles.

Liver.—Biliary secretion is considerably reduced, causing the stools to be pale or clay-coloured or jaundice may set in. An injection of morphine ($\frac{1}{6}$ gr.) increases the intrabiliary pressure from a normal of 0 to 20 mm. to 200 to 300 mm. of water, causing gastric pain and discomfort resembling biliary colic which disappears slowly with the effect of morphine on the central nervous system. This increased pressure is due to increased tone and spasm of the sphincter of the common bile duct and is relieved by the administration of amyl nitrite or nitroglycerine but not of atropine.

Heart and circulation.—In therapeutic doses it has very little effect on the heart except that it is slowed from stimulation of the vagal centre and slightly strengthened in force. This action is antagonised by atropine. The cardiac muscles are only indirectly affected by large doses through low blood pressure and asphyxia. But the circulation remains fairly good till the last ; in fact death in opium poisoning is *not due to the failure of the heart, but to the paralysis of the respiratory centre.* The blood pressure is not influenced in therapeutic doses, although there is flushing of the face and dilatation of the skin vessels. In toxic doses blood pressure falls due to vasomotor depression. During asphyxia the face becomes cyanotic and of purple colour due to the vessels remaining dilated. As asphyxia advances the pulse may become slow, while the blood pressure varies depending upon the vaso-motor centre and the heart. Since these effects can be abolished by aerating the blood sufficiently by artificial respiration they are the indirect results through the respiratory centre.

Respiration.—In small non-narcotic doses morphine will quiet the respiration, making it slow specially if it was quick and increase its depth if it was shallow. In larger doses it *depresses the respiration so that the rate becomes progressively slower*, and in poisoning the respiration be-

comes very slow, even down to three or four per minute. The individual respirations eventually become shallow and irregular and before death may assume **Cheyne-Stokes** type or **Biot's** type. According to Barbour this results from depression of the centre and consequent asphyxia of the heart which leads to variation of the blood pressure and blood supply to the brain. During natural sleep and also in sleep following a hypnotic the breathing becomes slow because less oxygen is required for the inactive body, but the CO_2 content of the blood remains unchanged. In morphine poisoning the CO_2 content of the blood is increased and in large doses the respiratory centre loses its sensitiveness, and greater than normal percentage of CO_2 is required to bring about respiration. Morphine and its derivatives **depress** the expitability of the **respiratory centre.** Death takes place from paralysis of the centre and asphyxia. The cough centre is also depressed, in fact

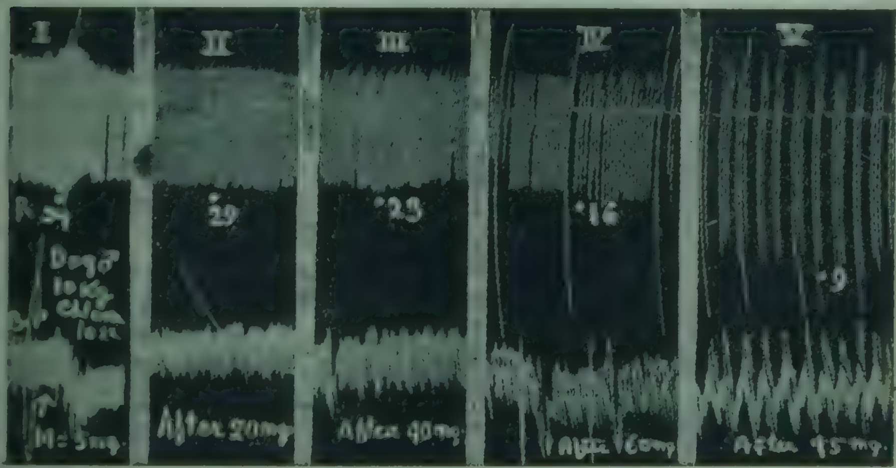


Fig. 5.—Dog under chloralose showing effect of morphine on respiration.

Note progressive slowing of respiration from 34 (1) to 9 (V) when breathing occurs at intervals alternating with periods of apnoea (Grouped Breathing) which, though not of Cheyne-Stokes type, resembles Biot type of respiration.

morphine, dionin and codeine reduce the sensibility of the cough centre in very small doses.

Bronchial muscles are slightly relaxed by therapeutic doses of morphine, but more powerfully by papaverine and narcotine. This relaxation is of value in giving relief in bronchial spasm. It is well to remember that the bronchial muscles are contracted in toxic doses. Unless there is nausea, the secretion of mucus is diminished, possibly due to suppression of cough and longer stay of the mucus in the bronchi, and consequent absorption of the water.

Nervous system.—The chief action of opium is on the central nervous system which is depressed, and because of

this there is apparent stimulation, no effect being observed on the peripheral portion. In this action it resembles alcohol and chloroform with this difference that it affects respiration and pain sensation in doses which have no effect on consciousness. In small doses, it first **excites the higher faculties.** During this stage, with a few the excitement is a pure exaltation of feelings, the imagination being pleasantly excited with a sense of happiness and comfort and the animal tendencies are set free. With others, the intellectual activity is heightened, and they can concentrate their energies better on a particular object. But in the majority of cases excitability is not uniform. In doses sufficiently small to elicit any other symptom the chief effects are diminished sensibility, especially to pain sensation, cough, fatigue, hunger, and other disagreeable sensations. In large doses attention is distracted and there is lessened appreciation of external impression and other disturbing factors thus promoting a dreamy abstracted state of mind conducive to sleep. After waking there is a feeling of headache and nausea. During profound sleep a sudden stimulus, like pricking or flicking a wet cloth on the body, may evoke a normal or exaggerated reflex, but gradual stimuli are not felt or appreciated, rather neglected. The stimuli though transmitted to the brain do not fix the attention. In this stage, the higher psychical centres are first depressed and then the lower ones. In fact opium acts on the cerebral centres in the reverse order of their development and forms an illustration of the "law of dissolution". Morphine has a specific action in relieving pain in non-narcotic doses which it does by depressing the tracts by which the pain sensations reach the consciousness. If the dose is large, the excitement is only momentary or absent. In toxic doses coma supervenes with a profound depression of the cerebrum and reflex excitability.

The *medullary centres* are affected by morphine ; the vagal and the vomiting centres are stimulated, while the respiratory and the cough centres are depressed. The vaso-constrictor centre is slightly stimulated but the vessels of the skin and head and neck region dilate. In large doses however there is depression of the vomiting centre so that no emesis occurs even after large doses of emetics. The oculomotor centre is stimulated causing contraction of the pupil.

Spinal Cord.—Both morphine and opium, more particularly the latter, increase the reflex excitability of the cord. In lower animals, e.g. frogs and cats, this is more marked and may be followed by convulsion of the strychnine type. In man the reflexes are depressed, but no muscular relaxation is noticed as happens after chloral or

bromides. Sometimes however it produces convulsion in man, but how far this is due to asphyxia or to morphine is difficult to say.

Nerves and muscles.—The motor and sensory nerves are not affected except in very large doses. There is no complete loss of muscular power or irritability, for even in severe opium poisoning, the patient can be made to walk if supported. Because of sluggish cerebral activity and diminished perception voluntary muscular activity becomes sluggish and there may be some inco-ordination.

Autonomic nervous system.—Morphine inhibits the enzyme choline esterase resulting in cholinergic stimulation. On the other hand there is increased secretion of adrenaline resulting in hyperglycaemia.

Uterus.—Barbour has shown that in therapeutic doses opium has no effect on normal uterine contraction of the animal. During labour it delays its progress because of the sedative action and by preventing reinforcement of labour pain by the contraction of the abdominal muscles.

Temperature.—It reduces temperature by loss of heat from dilated peripheral vessels, diaphoresis, and partly from diminished movements by which less heat is formed.

Eye.—In morphine poisoning the pupils are contracted to a pin point, and they are contracted even in small doses. The effect lasts till asphyxia sets in when they are widely dilated. The action is central, since when dropped into the eye or injected into the excised eye it has no effect. It has been shown recently that myosis is potentiated by neostigmine through an action on the 3rd nerve, thus indicating cholinergic effect.

Kidneys.—The secretion of urine is not affected by opium, although there is some retention of urine from spasm of the sphincter of the bladder in toxic doses. Morphine is found unchanged in the urine. There is a chance of morphine being reabsorbed from the bladder. The amount of sugar in diabetic urine, but not hyperglycaemia, is diminished.

Skin.—Opium is a **diaphoretic,** even in small doses, acting by dilating the cutaneous vessels. Before death there is copious perspiration due to asphyxia. It may cause itching and a rash.

Secretion.—It diminishes every secretion of the body except that of the skin and the mammary glands. There is however no conclusive evidence that the child is poisoned when given to nursing mother. Since it passes through the placental circulation to the foetus, the latter may be killed in utero.

Absorption and clearance.—Morphine is rapidly absorbed from all mucous surfaces and abraded skin. Its absorption from the intact skin is doubtful. From the

blood the drug absorbed passes into the tissues where it is temporarily stored. About 10 p.c. is excreted unchanged in the urine, the remaining 90 p.c. is broken down in the body. It is excreted by the gastro-intestinal tract even when used hypodermically and continues to be found in the stomach all through the period of morphine action. Traces have also been found in the milk and sweat.

It has been shown recently that the kidneys form the chief route of excretion of morphine, only a small amount being eliminated by the faeces. It is excreted as "free" and "conjugated" or bound morphine. The "free" form is excreted in equal amounts by both the tolerant and non-tolerant animals, it is only the "conjugated" form which is eliminated in less amount by the tolerant animal. Low percentage of excretion of "conjugated" morphine is characteristic of tolerant animals.

Toleration.—It is well-known that continued use of opium or morphine induces tolerance of the drug so that larger doses are necessary to elicit the desired effect.* Moreover, the patient can take quite a large dose without showing any untoward symptom. The same tolerance of the drug can be developed in animals (except rabbits), notably in monkeys, cats and dogs. The mechanism which enables the addict to tolerate large doses has not been clearly explained. It is possible that more than one factor is responsible for this phenomenon. It may be either storage of the alkaloid in the muscles or increased power of the tissues to destroy the alkaloid. The view that it is stored as oxydimorphine is not accepted as it has been shown that this compound is not formed. Similarly the idea that it helped the formation of antitoxin may also be dismissed as it has been found that blood of habituated animals contained neither protective nor toxic substances. Several workers have reported increased destruction of the alkaloid but it is doubtful whether this plays any important part in the production of tolerance. Recent experiments however show that there is diminished excretion of "conjugated" morphine.

Acute toxic action.—Poisoning by opium is very common in India, especially in Bengal. It is chiefly suicidal. Drowsiness and stupor soon follow. The patient may be roused at first, but soon passes into profound coma, and no external stimulus can rouse him then. The **pupils contract to a pin point,** surface becomes cold and clammy; face and lips livid; pulse very weak and slow; respiration slow, irregular and at the end stertorous; finally the patient dies from asphyxia. A few minutes before death, pupils dilate.

Treatment.—If opium or morphine is swallowed, wash out the

* This form of tolerance is known as *acquired tolerance* or *Mithridatism.* The story goes that Mithridates, king of Pontus, made himself immune to all possible poisons in this way, to make himself as it were poison-proof.

stomach with stomach-pump, emetics generally fail after absorption owing to depression of the centre. Potassium permanganate is a chemical antidote and its solution (4 to 8 grs. in 4 to 8 ozs. of water) should be given at once if the quantity of poison is unknown or large, before washing. A weak solution should be employed as a wash for the stomach. The special danger is the failure of respiration, therefore respiratory stimulants in the form of hot black coffee (caffeine) should be used. Atropine 1/40 gr. should be given to excite the centre but in larger doses it tends to weaken the respiration. Carbon dioxide and oxygen inhalation. Because of their special action on the respiratory centre, leptazol and nikethamide may be injected. Strychnine 1/60 gr. hypodermically, repeated every 2 or 3 hours. Similarly, artificial respiration. Use of "Iron Lungs" is helpful. Alternate cold and hot affusions, flagellations, or taps upon the forehead with finger-nails, sinapism, electricity, smelling salts to the nose, and making the patient walk to and fro, should be adopted to keep the patient awake. The treatment is to be kept up for several hours until the danger is over.

Chronic toxic action or Morphinomania.—Persons soon get habituated to the use, and can consume large quantities. It is therefore necessary that the patient should remain ignorant of the drug. India, Turkey, Persia, and China are the principal countries where the drug is habitually indulged in. Morphinomania exists also in England. In India opium is either eaten or smoked. Moderate doses (5 to 20 grs.) daily do not harm, but *madak* and *chandu* smokers are a disreputable set. Moral depravity, emaciation, anaemia, muscular weakness, physical depression, feeble and small pulse, tremor, slight ataxy, loss of appetite, indigestion, sluggish bowels, insomnia, drowsy feeling, sexual impotence, amenorrhoea, small pupils, are the principal symptoms of morphinomania.

Modifying influences.—Many circumstances modify the action of opium. (1) *Age.*—Children are more susceptible to poisoning. An infant under one year should not have more than 1/2 to 1 m. of the tincture. (2) *Sex.*—Women suffer more from after-effects than men. To a nursing mother it should be given with caution. (3) *Idiosyncrasy.*—Some cannot take opium without brain symptoms, such as insomnia or delirium, while others suffer from gastric irritation. (4) *Habit.*—Toleration is readily induced, when large doses become necessary to produce the desired effect and gradually lead to *opium habit.* (5) *Disease.*—Acute painful diseases require larger doses. Subjects of Bright's disease cannot bear much opium, and it should be given to them with great caution, also to persons suffering from cardiac, pulmonary, and renal diseases, cerebral congestion and alcoholism. (6) *Drugs.*—Chloral hydrate, potassium bromide, chloroform, etc., increase its soporific virtue, while belladonna removes constipation when given in combination.

Difference of action between opium and morphine.—Though the description of the pharmacology of opium given in these pages applies also to that of morphine, yet there are certain differences, which are detailed below.

Opium	Morphine
1. Preparations less soluble, slowly absorbed. Action slow, but more lasting.	Preparations more soluble, readily absorbed, action quicker, but not so lasting.
2. Its several constituents, such as thebaine, codeine, narcotine are convulsants.	Morphine not so in man.
3. Action variable on account of varying composition.	Action definite on account of definite composition.
4. Constipation, nausea, and indigestion more frequent.	Constipation, nausea, and indigestion less frequent.
5. Better diaphoretic.	Feeble or no diaphoretic.
6. Less sedative and less soporific.	More sedative and more soporific.
7. Greatly reduces the sugar of diabetic urine.	No appreciable effect.

Opium	Morphine
8. Local action more marked on the intestines.	Less marked on the intestines.
9. Cannot be administered hypodermically.	Can be administered hypodermically.

Antagonists.—Atropine, caffeine, cocaine, and strychnine are antagonistic to some action or other of morphine. The antagonism between morphine and atropine is given below in detail.—

	Morphine	Atropine
Real	1. Cerebral convolutions depressed.	Cerebral convolutions stimulated.
	2. Respiratory centre depressed.	Respiratory centre stimulated.
	3. Intestinal peristalsis depressed causing constipation.	Intestinal peristalsis regulated. No constipation.
Apparent	4. Stimulates the vagus centre and *slows* the pulse.	Depresses the vagus nerve endings and *quickens* the pulse.
	5. *Pupils contracted* through the effect on the pupillary centre.	*Pupils dilated* through the paralysis of the third nerve endings.
	6. *Diaphoretic* by dilating the cutaneous vessels.	*Anhydrotic* through the terminal nerves in the glands.

Though morphine and atropine are not true antagonists, yet they are useful antidotes to each other in poisoning. They are therefore partial antagonists and are used in combination to avoid certain untoward results of morphine without losing the useful effects. They are useful in combination in renal and hepatic colic, both of which relieve spasm, and atropine obviates the nausea which follows the use of morphine alone.

THERAPEUTICS

Externally.—Opium is chiefly used as a local sedative and anodyne. Hot poultices or fomentations containing opium or with laudanum sprinkled, are often employed to relieve the pain of pleurisy, rheumatism, peritonitis, lumbago, inflamed joint, etc. *Earache* is relieved by laudanum mixed with equal amount of glycerin. Opium or morphine suppository, and the gall and opium ointment often allay the pain of anal fissures and piles. The suppository relieves rectal tenesmus, urethral spasms, or pelvic pains. Neuralgic pains are better relieved when morphine is used hypodermically.

Internally.—Opium is a remedy *par excellence* for removing pain, subduing excitement and irritation, and inducing sleep.

Mouth and stomach.—Opium or morphine allays **gastric pain.** Thus it is very useful in ulcer, cancer, and gastritis produced by alcoholism. Morphine with bismuth markedly relieves gastrodynia with or without heart-burn.

Intestines.—Of all the drugs we have for **diarrhoea** opium is the most valuable both in the acute, chronic and tubercular varieties. It is desirable to administer one or two doses of opium in diarrhoea or dysentery after the expulsion of the offending matters. It is usually combined with bismuth in diarrhoea* and castor oil in dysentery. In the early stage of cholera, especially when

* Bism. carb.	grs. 10
Pulv. ipecac. et opii	grs. 5
Pulv. cret. aromat.	grs. 10

preliminary diarrhoea is the prominent symptom, opium may be usefully employed,* but not in the cold stage. It relieves **intestinal colic** caused by sharp aggravated contractions of the bowels. In **peritonitis** it is of special value as it not only relieves pain and restlessness but also diminishes movements of the intestine. Here opium is better than morphine.

Enema Opii (0.5 to 6 p.c. in mucilage of starch) 2 to 4 ozs. is serviceable in various ways, by checking flux, subduing local irritation, pain and spasm of the rectum and neighbouring structures, and giving rest to the pelvic organs. A morphine suppository generally averts a rigor likely to follow catheterisation or abdominal operations. To soothe the local pain, an ordinary dose is enough for rectal injection, but a large dose is required to induce sleep.

Heart and blood-vessels.—Opium, preferably morphine, is sometimes used in diseases of the heart. Both morphine and dilaudid are indicated in the treatment of **coronary occlusion** where they control excruciating pain of the disease. Relief is often afforded in dyspnoea of heart disease and of blood-vessels, and in **angina pectoris.** A single injection of $\frac{1}{6}$th gr. brings on refreshing sleep from which the patient wakes up wonderfully revived ; but it should not be used in cardiac dyspnoea caused by the pressure of serous and dropsical fluid. If the kidneys are diseased opium is said to be contra-indicated though many recommend the administration of morphine ($\frac{1}{6}$ gr.) subcutaneously in renal dyspnoea and uraemic convulsions. Atropine may be usefully combined to counteract the depressing effect.

Morphine is valuable in internal haemorrhage particularly in **intestinal** and **pulmonary bleeding.** In the former, it is of special value because of its action on the movements of the intestine ; and in the latter, it not only slows the heart and reduces blood pressure, but lessens cough, produces sleep, and removes mental anxiety, thus promoting conditions favourable for arresting haemorrhage. It has no action either on the vessels or blood, *i.e.* the effect is indirect.

Respiratory tract.—Opium relieves *cough* but should be used with judgment. When the cough is harassing and frequent, without much expectoration and without any tendency to asphyxia or lividity, due to reflex irritation or from excessive irritability of the nerves as in pleuritis, opium is justly and admirably indicated. But, when the act of coughing is only to empty the bronchial

*Acid sulph. aromat.	ms.	10
Tinct. chlorof. et morph. co.	ms.	5-10
Syr. zingib.	ms.	30
Aqua menth. pip.	ad. oz.	1

In early stage of cholera.

tubes of the abundant secretion, as in the bronchitis of the aged and infirm, or of the weak and young, opium is injurious: as by depressing the cough reflex it will cause retention of the mucus and may aggravate dyspnoea or even precipitate asphyxia. In phthisis where the tubercles press upon the nerves, and give rise to reflex cough, opium may be given with benefit. In the same way, in the form of linctus (*see* p. 176) and lozenges, many reflex coughs can be relieved. Sometimes it gives marked relief to the spasm in **whooping cough**; $\frac{1}{4}$ to 2 ms. of the linctus every hour, or $\frac{1}{50}$ gr. of morphine every 3 or 4 hours, according to the age of the child, should be continued until the whoop disappears. It should be given with great caution in **asthma**, lest it should create opium habit. The sharp stitch of **acute pleurisy** or **pleuro-pneumonia** is relieved with a hypodermic injection of morphine. It may be used in the early stage of pneumonia to relieve pain and distress, but should be avoided in the later stage specially when there are signs of respiratory failure. A dose of Dover's powder often cuts short an attack of acute coryza and gives relief in influenza when taken with acetylsalicylic acid.

Nervous system.—As a **hypnotic**, pure and simple, morphine is inferior to chloral hydrate, but for sleeplessness due to pain or irritation, it is a sovereign remedy. It is often used in the insomnia of acute diseases, in mania and delirium tremens and is often combined with bromides. A hypodermic injection of morphine ($\frac{1}{4}$ to $\frac{1}{2}$ gr.) relieves biliary, renal and intestinal colics; sciatica; facial, and other kinds of neuralgias; and severe pleurodynia. The pain of fractures, dislocations or other injuries, of acute rheumatism, dysmenorrhoea and malignant diseases are only a few instances where opium or morphine can be most usefully employed. In short any pain, inflammatory or otherwise, is relieved by opiates. It is to be noted that sufferers from pain can tolerate large quantities without poisoning.

As an antispasmodic in convulsive diseases it has been used in tetanus and other forms of convulsions, such as chorea and epilepsy, but it is doubtful if it is of any use in these diseases since morphine itself increases reflex excitability. Moreover, its depressant effect on the respiration should be kept in mind. In these diseases drugs of the chloral group or any of the barbiturates are preferable. The pains and spasms of certain diseases of the cord, such

Pot. bicarb.	grs. 10
Tinct. opii camph.	ms. 20
Sp. ammon. aromat.	ms. 20
Syr. prun. serotini	ms. 30
Aqua chlorof.	ad. oz. 1

In chronic bronchitis and cough

Ammon. chlorid.	grs. 5
Tinct. ipecac.	ms. 7½
Tinct. opii camph.	ms. 20
Syr. scill.	ms. 30
Aqua chlorof.	ad. oz. 1

In bronchitis.

as locomotor ataxy, are subdued by the subcutaneous injection of morphine.

Because of the depressant effects on the brain, morphine is valuable as a **preanaesthetic hypnotic** and is given prior to an operation (*see* page 168). It also potentiates the action of volatile anaesthetics when it is combined with atropine. It relieves pain, diminishes anxiety and excitement making anaesthesia smooth and more rapid ; moreover the amount of anaesthetic used is less, and thus lessens chances of pulmonary and other complications. On the other hand it is constipating and plays a significant rôle in the incidence of post-operative ileus. Respiratory depression may coincide with that of deep surgical anaesthesia. When combined with scopolamine it produces sufficient anaesthesia to perform operations. For this purpose morphine ($\frac{1}{6}$ gr.) and scopolamine ($\frac{1}{200}$ gr.) is given in two injections. This combination has also been used during labour, the so-called "twilight sleep."

Kidneys.—As morphine is not rapidly eliminated by the diseased kidneys, it should be given with caution in Bright's disease, for instances have occurred where small doses have produced fatal results. But a hypodermic injection of $\frac{1}{4}$ gr. of morphine has occasionally been found to remove uraemic insomnia, uraemic convulsions and uraemic or cardiac dyspnoea, and one is justified in taking this risk under these conditions. As they reduce the sugar in diabetic urine, opium and codeine are used in **diabetes mellitus.**

Skin.—As a diaphoretic, Dover's powder is used in a variety of diseases, such as cold, influenza and slight inflammatory conditions.

Uterus.—Opium is invaluable in arresting a threatening abortion. It must be given in large doses, the tincture in 20 or 30 ms. doses every 3, 4 or 6 hours, as indicated. In normal labour its use should be confined to the first stage. In later stage it is better avoided as there is risk of depressing the respiratory centre of the child. It is also used to relieve after-pains.

Malaria.—It has been noticed that opium-eaters are less liable to malarial infection, and they enjoy better health in a malarial district. Opium occasionally cures malarial fever where quinine fails, or the two drugs combined are more successful than either given alone. This effect is possibly due to *narcotine* which is used in chronic cases either alone or with quinine.

Contra-indications.—It should not be used in

(*a*) oedema of the lungs, and Cheyne-Stokes breathing ;

(*b*) inflammatory and congestive state of the central nervous system, *e.g.* meningitis, fever, in overwork and in cerebral congestion with a tendency to apoplexy ;

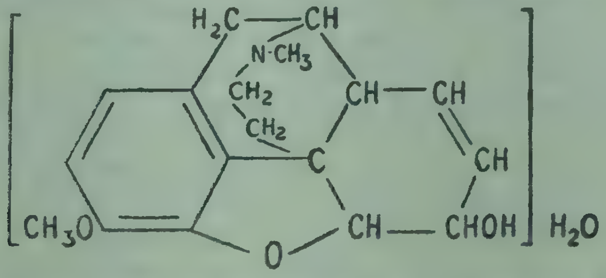
(*c*) acute dilatation (paralysis) of the stomach or bowels ; and *used with caution* in

(*d*) nephritis, especially when there is a tendency to uraemia ;

(*e*) infancy and old age ; and

(*f*) in all chronic painful diseases on account of the risk of formation of habit.

CODEINA. (Codein.). $C_{18}H_{21}NO_3,H_2O$. Syn.—Methylmorphine, U.S.P.—Codeine is morphine methyl ether, an alkaloid obtained from opium, or prepared by the methylation of morphine.



Characters.—Colourless, translucent crystals, or a crystalline powder ; odourless ; taste, bitter. *Soluble* in 120 parts of water, readily in alcohol (90 p. c.), in 75 parts of solvent ether, freely in chloroform.
B. P. Dose.—1/6 to 1 gr. or 10 to 60 mg.

Codeinae Phosphas. (Codein. Phosph.), $C_{18}H_{21}NO_3,H_3PO_4,H_2O$.—Codeine Phosphate is the phosphate of the alkaloid codeine.

Characters.—Colourless, acicular crystals, or a crystalline powder ; odourless ; taste, bitter. *Soluble* in 4 parts of water, in 350 parts of alcohol (90 p.c.) sparingly in solvent ether and chloroform.
B. P. Dose.— 1/6 to 1 gr. or 10 to 60 mg.

Official Preparations

1. **Tabellae Codeinae Phosphatis.—B. P. Dose.—1/6 to 1** gr. or **10 to 60** mg. N. B.—When no dose is given 1/2 gr. tablet should be supplied.
2. **Tabellae Codeinae Co.** *Syn.—Tablets of Aspirin, Phenacetin and Codeine.*—Contains 4 gr. each aspirin and phenacetin and 1/8 gr. codeine phosph. in each. **B. P. Dose.—1 to 2 tablets.**

Non-official Preparations

1. **Linctus Codeinae, B. P. C.**—Codeine Phosphate 1/8 gr. in 1 dr. Syrup of codeine phosphate 30 ms., syrup of wild cherry and syrup of tolu. each 15 ms. *Dose.*—1/2 to 1 dr. or 2 to 4 mils.
2. **Apocodeinae Hydrochloridum.**—A greyish powder soluble in water. Sedative and *increases intestinal peristalsis* by depressing sympathetic endings, therefore antagonises action of atropine. *Dose.*—1/10 to 1 gr. or 6 to 60 mg.
3. **Dicodid.**—Dihydrocodeinone acid tartrate. Similar to dilaudid. Also makes the respiratory centre less sensitive to CO_2 *Dose.*—1/16 to 1/12 gr. or 4 to 5 mg.
4. **Syrupus Codeinae Phosphatis, B. P. 1914.**—Codeine phosphate, 5 grm. ; distilled water, 20 mils ; syrup, q.s. 1000 mils. Strength 1/4 gr. in 1 dr. *Dose.*—1/2 to 2 drs. or 2 to 8 mils.

Pharmacology

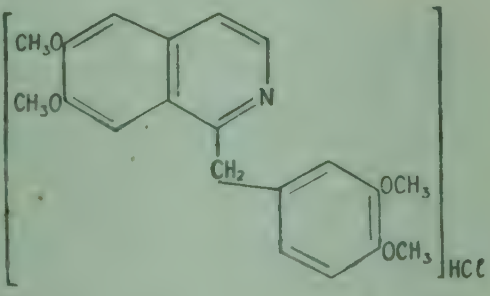
Internally.—Codeine is a feeble narcotic, because it does not depress the cerebral convolutions so actively as morphine, but it excites the cord more producing muscular tremor and increased reflex excitability when used in slightly beyond the hypnotic dose. It is therefore inferior to morphine in relieving pain and producing sleep. It does not produce nausea or vomiting, but causes constipation. It does not cause a habit, and is less depressing to the respiration than morphine, but it will relieve cough in doses insufficient to relieve pain. It is a great paralyser of the visceral nerves. It lessens the amount of sugar in diabetes.

Therapeutics

Internally.—On account of its sedative effect on the visceral nerves, it soothes the hacking cough of phthisis and visceral neuralgia.* Syrup of codeine phosphate in 1 to 2 dr. doses, alone or with syrup of wild cherry, is a good preparation for allaying cough. Sometimes it is used with advantage in insomnia due to pain in some peripheral regions, when it should be given in 1 or 2 gr. doses, every 4 or 6 hours, till sleep comes on. But its chief use is in the treatment of **diabetes mellitus**† in which case it can be given in the form of a pill. The phosphate being more soluble than the alkaloid can be used in a mixture. It is highly efficient in abdominal and pelvic pain, specially when ovarian in origin.

Apocodeine resembles apomorphine in its action, but is a better expectorant and less efficient emetic than the latter. 30 ms. of a 1 p.c. solution is used in bronchitis, and the same amount when used hypodermically acts as a purgative.

PAPAVERINAE HYDROCHLORIDUM. (Papaver. Hydrochlor.).—**Papaverine Hydrochloride is the hydrochloride of an alkaloid, papaverine, obtained from opium, or prepared by synthesis.**



Characters.—White crystals, or white crystalline powder ; odourless ; taste, slightly bitter. *Soluble* in 40 parts of water, soluble in alcohol (90 p. c.), and in chloroform.

B. P. Dose.—2 to 4 grs. or 0.12 to 0.25 grm.

Action and Uses

Papaverine is absorbed from the stomach and is probably destroyed in the liver, very little being detected in the urine or stool. Its action on the central nervous system is between codeine and morphine but does not possess the sedative effect of morphine. It is a direct depressant to all forms of smooth muscle and lowers blood pressure by vaso-dilatation chiefly of the splanchnic area. Its action on the heart is indirect through dilatation of the coronary artery. It diminishes the sensibility of the auricle and ventricle to faradic current thus reducing its susceptibility to premature beats and fibrillation. Moreover it prolongs the refractory period of the heart.

Papaverine is used to relax vascular spasms in coronary occlusion, angina pectoris, Raynaud's disease and in pulmonary embolism. It may be administered by the mouth but in urgent cases should be used either intramuscularly or intravenously. Because of its antispasmodic property it has been used in bronchial and visceral spasms, but the results have not been very satisfactory in these conditions.

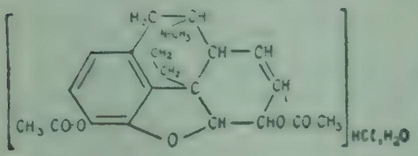
* Codein. phosph.	gr. 2
Syr. prun. serot.	ms. 180
Syr. scill.	ms. 180
Glycerin.	ms. 120

1/2 to 1 teaspoonful for cough.

† Codein. phosph.	gr. 1/2
Ext. nuc. vom. sicc.	gr. 1/4
Ext. bellad. sicc.	gr. 1/4
Pil. rhei co.	gr. 3

It has however given satisfactory result in spasm of the biliar ducts.

DIAMORPHINAE HYDROCHLORIDUM. (Diamorph. Hydro chlor.). $C_{21}H_{23}O_5N,HCl,H_2O$.



Syn.—Heroin Hydrochloride; D acetylmorphine Hydrochloride.- Diamorphine Hydrochloride is th hydrochloride of an alkaloid ob tained by acetylation of morphine

Characters.—A colourless, crystalline powder; taste, bitter. *Solubility.*—1 i 2 parts of water, 1 in 11 parts of alcohol (90 p.c.).

Incompatibles.—Acids and alkalies which decompose it.

B. P. Dose.—1/12 to 1/6 gr. or 5 to 10 mg.

Non-official Preparations

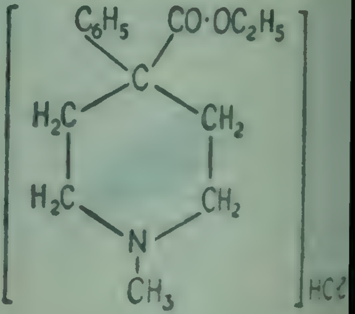
1. **Elixir Diamorphinae et Pini Co., B. P. C.**—Each dr. contains 1/40 gr. dia morphine hydrochloride, and 1/4 gr. terpin hydrate with oil of pine, glycerin etc. *Dose.*—1/2 to 1 dr. or 2 to 4 mils.
2. **Elixir Diamorphinae et Terpini, B. P. C.**—Contains 1/20 gr. heroin hydro chlor, and 1/4 gr. terpin hydrate, in 1 dr. *Dose.*—1/2 to 1 dr. or 2 to 4 mils.
3. **Linctus Diamorphinae et Hyoscyami, B. P. C.**—Diamorph. hydrochlor. 1/2 gr., tinct. hyoscy. and chloroform emulsion, each 4½ ms., syrup of tolu and wil cherry, each 9 ms., glycerin q.s. 60 ms. *Dose.*—30 to 120 ms. or 2 to 8 mils.

Pharmacology and Therapeutics

Heroin resembles morphine in its general action which it has replaced in the treatment of cough, especially the dry hacking cough of phthisis. It acts more power- fully on the medulla and cerebrum and therefore more toxic. It is a depressant to the respiration, which is ren- dered slower but deeper, but it does not interfere with gas exchange. It is about five times more depressant than morphine, but less so to sensory nerves and not so consti- pating. A hypodermic injection often relieves a fit of asthma. For the relief of cough it is generally used in the form of linctus. It is liable to produce a 'habit' and causes suppression of urine, and has no advantage over morphine or codeine.

PETHIDINAE HYDROCHLORIDUM. (Pethidin. Hydrochlor.)

Syn.—Demerol, Dolantin.—Pethidine Hydrochloride is the hydro- chloride of ethyl 1-methyl-4-phenyl- piperidine-4-carboxylate. Contains not less than 99.0 p. c. of $C_{15}H_{21}O_2N$, HCl.



Characters.—A colourless, crystalline powder; odour, faint; taste, bitter. Very *soluble* in water, less so in alcohol (90 p.c.), soluble in chloroform, sparingly in acetone and solvent ether.

B. P. Dose.—2/5 to 1⅓ gr. or 25 to 100 mg.

Official Preparation

1. **Injectio Pethidinae Hydrochloridi.**—**B. P. Dose.**—2/5 to 1⅓ gr. or 25 to 100 mg.

Action and Uses

Pethidine combines the effects of atro- pine, papaverine and morphine. It re- sembles atropine on the pupil, heart, bronchi and vagus in its pharmacological actions, while it resembles papaverine as antispasmodic on the bronchi, the intestines and the

blood vessels. For its euphoric properties, and as a sedative and analgesic it resembles morphine, but is less powerful.

Pethidine therefore is used as an **analgesic** and **antispasmodic** in the intestinal, biliary and renal colic, and as an analgesic in sciatica and other forms of neuralgia and to relieve **post-operative pain and spasm.** It has also been used as a **preoperative anaesthetic**, and in this respect it is superior to morphine since respiration is less affected and urinary retention is less common. It potentiates the action of barbiturates and provides a more pleasant induction, while at the same time, the amount of general anaesthetic required is lessened. Since it reduces the sensitiveness of the cough centre it is used to **relieve cough.** It has also been recommended as an analgesic and for its antispasmodic action on the cervix during labour. 0.1 grm. (1½ gr.) is *injected intramuscularly* when the cervix is two fingers dilated, followed after an hour by another similar dose combined with 1/160 gr. (0.4 mg.) of scopolamine.

Untoward effects.—Vertigo, induration at the site of injection, nausea, vomiting, paraesthesia, sweating and rarely insomnia, dimness of vision and delusion. It is liable to addiction because of its euphoric effect.

AMIDONE. (Not official). **Syn.**—Methadone ; Physeptone ; Dolophine.—It is 6-dimethylamino-4, 4-diphenyl-3-heptanone hydrochloride. A white crystalline substance soluble in water and alcohol. Taste, bitter.

USES.—It is a powerful **analgesic**, 5 to 10 mg. (1/12 to 1/6 gr.) being as effective in relieving pain as 15 mg. (1/4 gr.) of morphine or 150 mg. (2½ gr.) of pethidine. Like morphine it depresses the respiratory and cougn centres ; causes myosis and constipation, but to a lesser degree. In ordinary doses, it is neither a sedative nor a hypnotic and therefore cannot be used as pre-anaesthetic medication. It is very effective in relieving **post-operative pain, dysmenorrhoea, renal colic** and also **cough.** It is, however, of little value in controlling labour pain or pain of arthritis and of carcinoma. Amidone is also an effective substitute for morphine, in addicts in whom the withdrawal symptoms of morphine can be relieved or prevented by its use in doses much smaller than that of the previously administered morphine.

Analgesic action usually develops in about half an hour after oral administration, in 15 to 20 minutes after subcutaneous injection and usually lasts for 2 to 4 hours or more.

Administration and Doses.—Oral use is almost as effective as when used subcutaneously.

For moderate pain,—2.5 m.g. (1/24 gr.) *orally* every 3 or 4 hours and also to relieve cough. *For severe pain,*—5 mg. (1/12 gr.). *For acute excruciating pain,*—10 mg. (1/6 gr.) *subcutaneously.*

Toxicity.—Side effects are usually more evident in ambulant than in non-ambulant patients and as a rule less than with morphine. Chief side effects are nausea, vomiting, headache, myosis, drowsiness or euphoria and dry mouth. Most effective dose producing minimum side effects is 7.5 mg. There is a chance of developing tolerance to its analgesic action when used in very large doses but not in therapeutic doses even when used for a prolonged period. In morphine addicts, when the drug replaces morphine, there is also a tendency for the drug itself to form habit and even there may be unpleasant symptoms following withdrawal of the drug but these symptoms are mild and develop slowly compared with those of morphine and usually subside in about ten days.

CANNABIS, I.P.L. (Cannab.). **Syn.**—Cannabis Indica ; Indian Hemp. *Ganja*, **Beng.**

Source.—The dried flowering or fruiting tops of the pistillate plants of *Cannabis sativa*, grown in India, from which no resin has been removed.

Composition.—(1) An active *Resin* (*cannabinone*), the chief constituent o
which is *Cannabinol*, $C_{21}H_{26}O_2$ (2) *A Volatile Oil*. Fat, wax, etc.

Incompatibles.—Water and watery infusions precipitate the resin.

PREPARATIONS

1. **Extractum Cannabis, I. P. L.**—A rich green, soft resinous extract. *Dose.*—
1/4 to 1 gr. or 15 to 60 mg.
2. **Tinctura Cannabis, I.P.L.**—1 in 9 of extract. *Dose.*—1/2 to 1½ ms. or 0.0
to 0.1 mil.
3. **Cannabinae Tannas.**—A brownish powder. In *dysmenorrhoea, menorrhagia*
and as a *hypnotic* in nervous insomnia. *Dose.*—4 to 8 grs. or 0.25 to 0.5 grm.

PHARMACOLOGY

Internally.—In small doses it **sharpens the appetite**, which be-
comes sometimes so ravenous that it cannot be appeased by food
It also **promotes digestion** and causes constipation. If indulged i
for long it may cause loss of appetite and gastric derangement. I
is slowly absorbed by the small intestine and produces its effect
within half an hour. It **relieves spasm** of the **intestine.**

Nervous system.—Its chief action is on the cerebrum and resem-
bles in many respects that of alcohol or opium, but is uncertai
owing to variation in strength and to individual peculiarities. Whe
smoked the effects are almost instantaneous. In small doses, eithe
smoked or taken by the mouth, it causes pleasurable sensation
with gay, joyful and exalted ideas and a refreshed feeling, speciall
after bodily fatigue. In fact it is often smoked by some people t
enable them to undergo physical exertion without appreciation o
fatigue or exhaustion. Ganja smoking is almost universal wit
certain classes of *sadhus* and *mendicants* and it is said it helps the
to forget all about their worries and privations of the outside world
and concentrate their mind in an agreeable manner to their devotion
Under its influence the knowledge of time and personality is los
and the drugged man feels that he is enjoying the pleasures of lif
for hours together, although in reality it is only for a few minutes
If continued, it causes intoxication and loss of self control. Th
subject becomes very talkative and jovial, and laughs at every thing
whereas a sedate person becomes more sociable, has less contro
over himself, and eventually passes into a sort of waking delirium
The delirium, generally noisy and restless, is accompanied by mus
cular excitement, and is followed by sleep which is attended wit
delightful and erotic dreams. It is therefore an **exhilarant, deliri
ant and hypnotic.** Sometimes there is considerable amount of heavi
ness in the head and the patient feels "a sensation as of the brai
boiling over and lifting the cranial arch." In large doses it induce
a sort of catalepsy, followed by coma and death from cardiac failure
Excessive smoking of ganja, specially by beginners may caus
mental derangement and even insanity.

The sensory nerves are paralysed and there is tingling and an
aesthesia of the skin. The muscular sense is also lost, and if pai
is present it is abolished or at least reduced. It is an **anodyne** bu
less so than opium or belladonna.

Heart and circulation.—Its action here is very uncertain. Th
pulse may be quickened or slowed depending upon excitation o
narcosis. The pulse is not altered when taken as a drink but be
comes slow during narcosis.

Respiration is not affected. The breathing becomes hurrie
during the stage of excitement.

The secretion of urine is slightly increased, but prepared *bhan*
which is used as a drink, causes copious **diuresis.**

In the form of *ganja*, hemp is largely smoked, and the leave
are used by powdering it and mixing with aromatics, sugar, carda
mom and milk, and the preparation is then known as *bhang, sidh*
or *sabji*. *Charas* is of a dark green or brown colour and contain
resins which exude from the leaves, is as a rule smoked with tobacc
and is a powerful narcotic. The leaves are also used in the prepara

tions of different kinds of sweets and pastries, and the prepared bhang is also taken as ice-creams. They all produce the same effects on the central nervous system. *Hashis* is a confection and contains in addition to the leaves and resins, opium, poppy seeds, datura seeds, cloves, anise, sugar, butter, milk, etc.

THERAPEUTICS

Externally.—Mixed with linseed meal (1 in 4), hemp in the form of poultice allays the irritation and pain of inflamed **piles and fissures.** The dry leaves warmed may be used as fomentation for the same purpose.

Internally. **Gastro-intestinal tract.**—As an appetiser and stomachic it is valuable in **dyspepsia and dyspeptic diarrhoea,** and relieves pain and spasm in dysentery, specially when combined with small doses of castor oil. It soothes the pain of gastralgia and **corrects the griping of purgatives.**

Nervous System.—As an *analgesic* it was largely used in migraine but is not much used now. It is occasionally used with benefit in continuous **headaches,** specially those occurring at the menopause, or due to worry and fatigue. As a hypnotic it is rarely used now although Sir Russell Raynolds strongly recommends the extract (1/4 to 1/2 gr.) in senile insomnia. As an anodyne antispasmodic, the tincture or the extract may be used in **intestinal, biliary and renal colics, spasm of the bladder and chordee.** Its beneficial effects in **tetanus** has long been recognised.

Genital organs.—In menorrhagia, spasmodic and nervous dysmenorrhoea and ovarian irritation, it not only relieves the pain, but seems to act favourably on the uterine muscular fibres.

2. ALIPHATIC HYPNOTICS

(a) Chloral Group

CHLORALIS HYDRAS

Chloral Hydrate. (Chloral. Hydr.). $CCl_3CH(OH)_2$

Source.—Obtained by the addition of water to chloral which is produced by the action of dry chlorine on ethyl alcohol.

Characters.—In colourless, non-deliquescent crystals. Odour, pungent but not acrid. Taste, pungent, bitter. Volatilises slowly on exposure to air. ***Solubility.***—**Less than in 1 part of water, alcohol (90 p.c.) and in solvent ether.**

Incompatibles.—Alkaline substances which liberate chloroform.

B. P. Dose.—5 to 30 grs. or 0.3 to 2 grms.

NON-OFFICIAL PREPARATIONS

1. **Butylchloral Hydras, B.P.C.**—In pearly white trimetric laminae, with a pungent acrid odour and an acrid taste. Action similar to chloral hydrate. Supposed to be specially valuable in neuralgia of the 5th nerve. *Dose.*—5 to 20 grs. or 0.3 to 1.2 grms.

2. **Glucochloral.** *Syn.—Chloralose.*—A hypnotic, resembles more morphine than chloral. Produces increased reflexes and sometimes convulsion, specially when large doses are given. Heart is not affected nor the respiration unless given in large doses. *Dose.*—3 to 10 grs. or 0.2 to 0.6 grm.

PHARMACOLOGY

Locally.—Chloral is an **irritant** to the skin and when used in a concentrated solution may even cause **vesication.** It is **an antiseptic.**

Internally.—Chloral is an irritant to the stomach and in concentrated solution causes **nausea** and **vomiting.** Given freely diluted no such effect is observed. It is readily absorbed and carried to the central nervous system **where it is taken up by the cells.**

Heart and circulation.—A moderate dose of chlora (10 to 20 grs.) in a healthy adult rarely causes any circulatory changes except that the heart is rendered slow, bu this is not more than is found in natural sleep. In commo with all narcotics containing a halogen derivative, it depresses the heart and finally arrests it in diastole, but thi effect is only observed when the dose is above the therapeutic limit. This is due to its direct action on the cardiac muscle. The blood pressure is not affected in ordinary therapeutic doses, but there is some flushing of th skin from dilatation of the cutaneous vessels, and for thi reason there may be skin eruption forming erythematou rash, although may be urticarial or purpuric. In larg doses, or in poisoning, the pressure falls from diminishe cardiac output and depression of the vaso-motor centr causing dilatation of the vessels, when the pulse become slow, feeble and intermittent.

Respiration.—In moderate doses no effect on respiration is observed, but in toxic doses the breathing become slower, shallower and irregular, and finally stops fron paralysis with the simultaneous arrest of the heart.

Temperature.—Chloral hydrate tends to lower th body-heat, and in toxic doses there is a marked **diminutio** of the **temperature,** due to dilatation of the cutaneou vessels and diminished production of heat from muscula relaxation, and possibly to diminished activity of the hea regulating centre.

Cerebrum.—In moderate doses (15 to 30 grs.) it induces within 10 to 15 minutes a sort of soothing drowsiness followed by refreshing sleep indistinguishable fron natural slumber. The sleep generally lasts from 5 to hours without producing any unpleasant after-effects such as, headache, drowsiness, confusion or sickness. I induces sleep by depressing the sensory or receptive func tions of the brain. And since the sleep is induced by dul ing of the perceptions, acute pain may prevent sleep afte chloral. In fact chloral has no effect in relieving pain lik opium. Large doses (30 to 60 grs.) cause prolonged slee which is deeper, and although no complete anaesthesia produced, pain is less felt and the reflexes are lessene Still larger doses produce stupor and coma with complet muscular relaxation leading to asphyxia from paralysis respiration. Before death the pupils are often contracte to pin point. The motor areas of the brain cortex a rendered less irritable which eventually fail to react electrical stimulation.

Spinal Cord.—In ordinary hypnotic doses the spin reflexes are not affected. In large doses they are fir depressed and then paralysed before the failure of respir

tion. This effect on the spinal reflexes is more marked than morphine.

Kidneys.—It is converted in the body into trichlorethyl alcohol which in the liver is transformed into urochloralic acid, an inert compound, by combining with glycuronic acid and excreted by the urine. Large doses cause nephritis and haematuria.

Absorption and clearance.—It is absorbed from all mucous surfaces and excreted with the urine as non-toxic trichlorethylglycuronic acid (urochloralic acid). It has less tendency to cumulative effect. A portion is eliminated unchanged. It escapes chiefly by the kidneys and partly by the lungs and skin.

Acute toxic action.—Acute poisoning is rare. The symptoms are profound sleep merging into deep coma; lividity of the face; pallor; cold sweat over the forehead and head; slow, laboured, and afterwards shallow and feeble breathing; frequent, feeble, and irregular pulse; *marked fall of temperature*, which may be so great as alone to cause death (Brunton); pupils contracted and absolute muscular relaxation. Death takes place from paralysis either of the heart or of the respiratory centre.

Treatment.—Emetics or pump. Friction; external warmth; stimulants, such as ammonia, ether, etc., atropine, strychnine, caffeine, leptazol and nikethamide hypodermically. The patient if he can be roused should not be allowed to sleep.

Chronic toxic action or Chloralism.—Craving for chloral is soon generated in those who are addicted to its use. Gastro-intestinal disturbance; cutaneous eruption, such as erythema, pustules, vesicles, etc.; bodily and mental weakness; sudden flushing, dyspnoea and palpitation are prominent symptoms. Death often results from an overdose. The best treatment is the gradual withdrawal of the daily dose with generous diet, fresh air, tonics and nervine sedatives such as hyoscyamus.

THERAPEUTICS

Externally.—As a *local anodyne* Chloral Camphor or Chloral c. Menthol may be painted over superficial neuralgic areas, and applied within carious painful teeth. The efficacy of any of these combinations may be greatly augmented by the addition of cocaine.

Internally.—As a *pure and simple hypnotic* it is unrivalled in sleeplessness due to worry, overwork or old age, but not to pain. In doses of 15 to 20 grs. it induces a refreshing sleep which thus obtained not infrequently leads to the repeated use of the drug and thereby induces the chloral habit. It is very efficacious in febrile insomnia. In fatty degeneration of the heart a hypnotic like paraldehyde, barbitone or soluble barbitone should be used, as they do not contain any chlorine molecule. In other affections of the heart, chloral may be used safely, and is often of great value as a hypnotic. It is a valuable remedy for **delirium tremens.** In combination with bromide of potash it will often check the disease in the early stages.

Because it depresses the motor area of the cord it i used in **convulsive diseases** of children and adults,* *vi* tetanus neonatorum, eclampsia, tetanus, strychnine poison ing, hydrophobia, etc., specially in combination with bro mides. The addition of a few drops of the tincture o Indian hemp gives very satisfactory results in tetanus. Many other **spasmodic affections,** such as chorea, asthma whooping cough, paralysis agitans and spasmodic intes tinal colic are benefited by it. It is an excellent drug fo lessening the rigidity of the os and other soft parts durin the first stage of labour without affecting the uterine con tractions.

As a *general anodyne* it is far inferior to morphin The difference between the actions and uses of chlora hydrate and morphine is given below :—

Chloral Hydrate	Morphine
1. A quicker, and a more refreshing hypnotic.	A slower, and a less refreshing hyp notic.
2. No after-effects, such as headache, depression, and sickness (sometimes heaviness or sleepiness only).	Always headache, confusion, an narcotism.
3. No constipation. No gastro-intestinal derangement in medicinal doses.	Constipation common and som times nausea.
4. Cannot relieve excessive pain nor induce sleep in insomnia caused by it.	Relieves pain and induces sleep i insomnia caused by it.
5. Cannot relieve reflex cough but can relieve convulsive diseases.	Relieves reflex cough, but not so us ful in convulsive diseases.

Caution.—It should be given with caution to old, gouty, rhe matic, hysterical, delicate and otherwise constitutionally wea persons. It should not be given to confirmed drunkards, exce when absolutely necessary for the treatment of delirium tremen It is contra-indicated in threatened failure of circulation, pneumon acute nephritis and gastric irritation.

Prescribing hints.—The aromatic syrup or syrup of ginger be covers its pungent taste. On account of its irritant effect it shou be used freely diluted, and should not be used either in the form tablets or pills, as when used in these concentrated forms it m irritate the stomach and the intestine. For the same reason it ca not be given hypodermically. It may be given by the rectum a is more effective than when given by the mouth. When prescrib with alkalies they decompose it and liberate chloroform. W camphor and menthol it forms an oily liquid and when given in so tion this liquid floats.

CHLORALFORMAMIDUM. **B.P.C.** (Not official). **Syn.**—Chloralamide—Colo less, inodorous, lustrous crystals. Taste, slightly bitter. *Solubility.*—1 in 21 water, freely in alcohol (90 p.c.), solution neutral to litmus.
Dose.—15 to 45 grs. or 1 to 3 grms.

PHARMACOLOGY AND THERAPEUTICS

Chloralamide resembles chloral in its action with this adv tage, that formamide, which is a stimulant, counteracts the depr sion of the circulation produced by chloral alone. It is less irrit

*Pot. brom. grs. 10
Chloral, hydr. grs. 10
Syr. aurant. ms. 30
Aqua chlorof. ad. oz. 1
As a hypnotic and in convulsion.

†Pot. brom. grs. 20
Chloral. hydr. grs. 15-20
Tinct. cannab. ind. ms. 5
Mucilage acacia q.s.
Aqua ad. oz. 1
In tetanus

to the stomach and kidneys than chloral, but is absorbed more slowly and after absorption is converted into chloral and is excreted partly as urochloralic acid. Chloralformamide may therefore be used as a **nervous sedative** wherever chloral is indicated. It takes about half to three-quarters of an hour to induce sleep, and some hold that it not only produces sleep but relieves pain. It is therefore of value in **neuralgia** and in relieving the pains of **locomotor ataxy**. Combined with bromide it has yielded good results in **sea-sickness**. It is incompatible with alkalies and should not be given with hot liquids.

CHLORBUTOL. $(CH_3)_2C(CCl_3).OH$. **Syn.**—Chloretone.—Chlorbutol is trichloro-*tert*.-butyl alcohol with a variable amount of water of crystallisation.

Characters.—Colourless crystals; odour and taste, characteristic, musty, and somewhat camphoraceous. Volatile at ordinary temperatures. *Soluble* in 125 parts of water, in 1 part of alcohol (90 p. c.), readily in solvent ether and chloroform; in 10 parts of glycerin, and in volatile oils.

B. P. Dose.—5 to 20 grs. or 0.3 to 1.2 grms.

Enters into.—Liquor adrenalinae hydrochlor.

Pharmacology and Therapeutics

Externally.—Chlorbutol is an **antiseptic** and a mild **anaesthetic** acting by paralysing the sensory nerve endings. An ointment with boric acid is used to soothe irritation and pain in **burns** and **scalds**, and to relieve **pruritus**, and an ointment or suppository (5 grs. each) is valuable in **inflamed piles**.* Dissolved in light liquid paraffin (1 p.c.) it is used as a spray in rhinitis, nasal catarrh, and sore-throat, and may be combined with menthol and camphor. Because of its antiseptic property it is used to preserve organic substances from decomposition, and it is added to adrenaline chloride solution for preservation.

Internally.—The action of chlorbutol resembles that of chloral except that it does not irritate the stomach. Being a gastric sedative, small repeated doses, either alone or combined with fractional doses of calomel, act as anti-emetic and check vomiting of pregnancy, sea-sickness, post-anaesthetic vomiting and vomiting of cholera.† It also stops vomiting by depressing the centre. It is a **hypnotic** in 10 to 15 gr. doses and is useful in nervous excitability; but is slower and less reliable than chloral hydrate. As an **antispasmodic** it is useful in hiccough, whooping cough, epilepsy and tetanus. In tetanus it may be given in 30 gr. doses dissolved in olive oil 1 dr. by **rectal injection**.

The usual method of administration is in powders, cachets or gelatin capsules. As it volatilises even at the ordinary temperature slowly, the powders should be dispensed enclosed in tinfoils and in stoppered bottles. When given in mixtures it should be suspended with acacia or tragacanth.

*Chlorbutol	grs. 20
Ung. Gall. c. Opio	oz. 1
Application for piles	

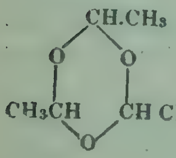
†Hydrarg. subchlor.	gr. 1/12
Chlorbutol	gr. 1
Lactose	grs. 5
To stop vomiting.	

(*b*) Aldehyde Alcohol Group

PARALDEHYDUM

Paraldehyde. (Paraldehyd.). $(CH_3.CHO)_3$

Source.—A product of the polymerisation of acetaldehyde.



Characters.—A colourless, transparent liquid ; odour strong, characteristic ; taste, disagreeable. *Solubility.*—1 in 9 of water ; miscible with solvent ether, chloroform alcohol (90 p. c.) and volatile oils.

B. P. Dose.—30 to 120 ms. or 2 to 8 mils. *For recta injection as a basal anaesthetic* : **1/2 to 1 oz.** or **15 to 3 mils.**

PHARMACOLOGY

Paraldehyde is readily absorbed, and manifests it action chiefly on the cerebrum, producing calm refreshing sleep, akin to natural slumber, without any after-effects or cardiac depression. It resembles alcohol in its effects but is a more powerful narcotic and rarely induces excitement. It is therefore a pure **hypnotic,** but its action is more speedy, producing sleep within ten to fifteen minutes As a hypnotic it is not so reliable as chloral hydrate, but is extremely safe, even a large overdose causing no more than prolonged sleep. In moderate doses it increases the flow of urine, without deranging the digestive tract, or affecting the cardiac or respiratory centres which are paralysed only by enormous doses, death taking place from respiratory failure. About 5 p.c. is eliminated by the breath, to which it imparts an unpleasant ethereal odour the rest is oxidised in the body. A roseolous rash is sometimes noticed on the skin.

Acute toxic action.—Poisoning from paraldehyde is rare. Two fatal cases have recently been recorded. In one a dose of 6 drs proved fatal, in another a total quantity of 2 ozs. taken during 3 hours proved fatal. Post mortem examination showed gastric mucosa hardened, wrinkled and greyish-white resembling the condition found in phenol or corrosive sublimate poisoning.* Two ounces given per rectum proved fatal.

THERAPEUTICS

Paraldehyde may be safely used as a **hypnotic** in insomnia of cardiac or respiratory diseases, mania, hysterica excitement, etc. It is used chiefly where chloral is contra-indicated, and is valuable in delirium tremens. Constant use may produce toleration.

Its action is short-lived and is useless in cases where prolonged sleep rather than speedy induction is required A paraldehyde habit though known is of rare occurrence Its only defect is the disagreeable taste and odour and that sometimes its use is followed by excitement and delirium

Since it is absorbed when given by the rectum, its use has been advocated as a **basal narcotic** preliminary to ad-

* *British Medical Journal,* Epitome, May, 1929.

ministration of some volatile anaesthetic. It is the safest of the basal narcotics and is therefore chiefly used for children. It is used dissolved in ten times its volume of solution in normal saline and is run into the rectum slowly at blood heat. It is usually given three-quarter of an hour before operation. The usual dose is 60 ms. for every stone of body weight. The solution used is paraldehyde 60 ms., normal saline 1½ oz., glucose 5 p.c. It is a safe drug and is free from undesirable after-effects. The patient falls asleep within 30 minutes ; it however sometimes produces excitement instead of narcosis. It is also used by the same route as a **sedative** in mania, eclampsia, tetanus and other convulsive diseases.

It has also been used combined with ether intravenously as a **general anaesthetic** for short operations, 1½ to 4 drs. with an equal amount of ether in 5 oz. of normal saline.

Prescribing hints.—Its pungent disagreeable taste is disguised by mixing it with syrup of orange and peppermint water, or by giving in capsules. Large doses should be emulsified with compound tragacanth powder. Remember that a small dose repeated within an hour is better than a single large dose. For rectal analgesia in labour, the required amount (60 ms. per stone of body weight) is mixed with 4 oz. of saline solution or olive oil. It is slowly injected into the rectum during the first stage after an enema taking 10 to 15 minutes over the process. Its use is not associated with any risk, either to the mother or the child. In cases in which the vertex is deep in the pelvis a soft catheter should be inserted per rectum above the level of the head.

ALCOHOL TRIBROMOETHYLICUM

(Alcoh. Tribromoethyl.). $CBr_3.CH_2OH$.

Syn.—Tribromoethanol.

Source.—Tribromoethyl Alcohol may be prepared by reduction of tribromoacetaldehyde. Contains not less than 99 p. c. of tribromoethanol.

Characters.—A white crystalline powder, unstable in air ; odour and taste, slightly aromatic. *Soluble* in about 35 parts of water at 25°C. Readily soluble in light petroleum and in amylene hydrate. Aqueous solution is unstable.

Amyleni Hydras. (Amylen. Hydr.). **Syn.**—Tertiary Amyl Alcohol.—Amylene Hydrate is dimethylethylcarbinol, and may be prepared by the hydration of amylene.

Characters.—A clear, colourless, volatile liquid at ordinary temperatures ; at temperatures below −12° forms hygroscopic acicular crystals ; taste, pungent and burning ; odour, characteristic, camphoraceous. *Soluble* in 8 parts of water ; miscible with alcohol (90 p. c.), with solvent ether, with chloroform, and with glycerin.

B. P. Dose.—30 to 60 ms. or 2 to 4 mils.

Bromethol. Syn.—Avertin.—Solution of Tribromoethyl Alcohol is prepared by dissolving Tribromoethyl Alcohol 66.7 grms. in Amylene Hydrate 33.3 grms. It contains, in 1 mil. 1 grm. of Tribromoethyl Alcohol.

B. P. Dose.—1/2 to 2/3 min. per lb. of body weight or 0.075 to 0.1 mil. per kg. of body weight. By rectal injection as a basal anaesthetic.

ACTION AND USES

Tribromoethyl alcohol is rapidly absorbed from the

rectum and induces **anaesthesia** within ten to twenty minutes without any excitement, and the patient returns to consciousness in sixty to ninety minutes. For production of general anaesthesia the drug is unsafe and therefore it is administered in 2.5 p.c. solution of bromethol in distilled water as a *basal anaesthetic* supplemented by light administration of ether, or nitrous oxide and oxygen. Maximum basal anaesthetic action is reached in from 20 to 30 minutes when its concentration in the blood is from 6 to 10 mg. per cent. Muscular relaxation varies with the dose and is complete in doses which produce surgical anaesthesia. With basal anaesthesia relaxation occurs when supplemented by ether or cyclopropane.

It is as a rule a safe basal anaesthetic and relatively free from post-operative complications. There is absence of mental distress and irritation of the respiratory tract. Moreover, only a small amount of volatile anaesthetic is required to complete the anaesthesia. It however causes some **toxic changes** in the liver, and fatal cases of acute yellow atrophy of the liver, resembling delayed chloroform poisoning, have been reported in animals.

The dose is regulated according to patient's weight. Children metabolise bromethol more quickly, therefore tolerate relatively larger doses. It should be administered after a bowel wash, twelve hours before the dose has to be given, with the patient lying on his left side with the foot of the bed a little raised. The injection should be given slowly taking about ten minutes and completed twenty minutes before the operation.

It causes fall of blood pressure and **depresses** the **respiratory centre,** which is greater than with chloroform or ether, and the centre becomes less sensitive to CO_2.

There is evidence that bromethol and thyroxine are in someway antagonistic to each other, and patients suffering from toxic goitre with high basal metabolic rates feel the greatest benefit of the drug. It is also suitable for nervous and excitable patients, during the second stage of labour, and to control the spasm of tetanus when used with specific antitoxic treatment.

Bromethol is soon detoxicated in the liver where it combines with glycuronic acid to form urobromic acid, in which form it is excreted in the urine.

Contra-indications.—(1) Patients with low basal metabolic rates ; they do not eliminate the drug freely ; (2) abnormally low blood pressure ; (3) when other drugs are used which lower blood pressure or depress the respiration, *e. g.* chloroform or morphine ; (4) in operations near the rectum or anus ; (5) any toxic condition ; (6) diseases of the liver and in nephritis ; and (7) in very young and cachectic children.

Note.—Bromethol is an unstable compound and should be used within an hour of its preparation and should be tested before use by

a few drops of 1 in 1000 solution of congo red; solution giving a red or orange-red colour should be used; if a blue colour develops, it implies presence of hydrobromic acid and should be discarded.

Amylene hydrate is a **hypnotic** and stands midway between paraldehyde and chloral, and is stronger than the former but weaker than the latter. In small doses it stimulates the central nervous system which is depressed in large doses, and causes a fall of temperature. It is used as bromethol to counteract the depressant effect of tribromoethyl alcohol when used as a basal narcotic.

(*c*) Sulphonal Group

These drugs owe their properties to the presence of alkyl radicals (methyl, ethyl, etc.). It has been found that the introduction of the radical ethyl C_2H_5 into an organic compound frequently confers upon it a sedative action and these become more powerful hypnotics.

SULPHONAL

Syn.—Sulphonemethane, U. S. P. $(CH_3)_2C(SO_2.C_2H_5)_2$.

Source.—Sulphonal is *Diethylsulphonedimethylmethane*.

Characters.—Colourless, prismatic crystals, or a white powder; odourless; nearly tasteless. *Soluble* in 450 parts of water, in 15 parts of boiling water; in 80 parts of alcohol (90 p. c.), in 90 parts of solvent ether, and in 3 parts of chloroform.

B. P. Dose.—5 to 20 grs. or 0.3 to 1.2 grms.

Pharmacology and Therapeutics

Sulphonal is a mild, slowly acting **hypnotic** and does not depress the heart or cause any disagreeable after-effects. It has no analgesic property and acts by virtue of its solubility in lipoids. It takes about four to five hours to produce sleep as its absorption is slow and uncertain, and sleep lasts for 6 to 8 hours and the effects may persist during the next day. It is very useful in simple insomnia, and may safely be given in heart disease. On the other hand, it is powerless when sleeplessness is due to pain and cannot produce that soothing effect on the brain which is induced by morphine.

It is excreted slowly and may have a cumulative effect, and its prolonged administration is sometimes followed by *haematoporphyrin* in the urine which makes the urine cherry red. This is more common with anaemic women and is accompanied by pain in the stomach, vomiting, weakness and ataxia, confusion, partial paralysis, suppression of urine, collapse and death. These symptoms appear several days after administration of the drug and may be after one or two weeks. There is danger of sulphonal habit. It is decomposed in the body and is found in the urine as ethyl sulphonic acid.

The administration is not without risk, when given to patients in a state of physical prostration, and alarming

symptoms have occurred after 20 gr. doses given to patients convalescent from influenza. *Restlessness, palpitation, giddiness*, and *confusion of thoughts* have occasionally been observed to take the place of sleep.

Prescribing hints.—Sulphonal may be given either in cachets or suspended in mucilage, but the best method of administration is to dissolve it in two-thirds of tumblerful of *boiling* water, or hot soup or milk and then stir until it is cool enough to drink. It should be taken at least four hours before bedtime.

Methysulphonal, B.P.C. (Not official). **Syn.**—"Trional".

Characters.—Colourless, lustrous scales, or a white powder ; odourless ; taste, slightly bitter. *Soluble* in 320 parts of water ; in 12 parts of alcohol (90 p. c.).
Dose.—5 to 20 grs. or 0.3 to 1.2 grms.

USES.—Methylsulphonal resembles sulphonal in its effects, but it is more prompt, inducing sleep in from 30 to 60 minutes and lasts for 8 or 10 hours. It is slightly cumulative, the toxicity appearing to increase in proportion to the increase in the ethyl groups. It has been largely used in **mental diseases** in which sulphonal has little or no effect.

(*d*) Urea Derivatives

Within recent years these derivatives have assumed an important place as hypnotics, analgesics and sedatives. They are related to urea which by combining with malonic acid forms barbituric acid or malonyl urea. The relationship of barbituric acid or malonyl urea is shown in the following formulae :—

$$CO < \begin{matrix} NH_2 \\ NH_2 \end{matrix} = \text{Urea}, \qquad CO < \begin{matrix} NH-CO \\ NH-CO \end{matrix} > C < \begin{matrix} H \\ H \end{matrix} = \text{Barbituric Acid.}$$

Barbiturates are formed by substituting alkyl or aryl groups for two H atoms of barbituric acid. Thus by substituting C_2H_5 we have Barbitone $= B < \begin{matrix} C_2H_5\text{—ethyl} \\ C_2H_5\text{—ethyl} \end{matrix}$ Phenobarbitone $= B < \begin{matrix} C_6H_5\text{—phenyl} \\ C_2H_5\text{—ethyl} \end{matrix}$

Allobarbitone $= B < \begin{matrix} C_3H_5\text{—allyl} \\ C_3H_5\text{—allyl} \end{matrix}$ Amytal $= B < \begin{matrix} C_2H_5\text{—ethyl} \\ C_5H_{11}\text{—isoamyl} \end{matrix}$

B = barbituric acid nucleus and is constant.

BARBITONUM

Barbitone. (Barbiton.). $C_8H_{12}N_2O_3$

Syn.—Malonurea ; "Veronal" ; Diethyl-malonyl-urea ; Barbital.
Source.—It is 5 : 5-diethylbarbituric acid, obtained by the condensation of ethyl diethylmalonate with urea.

Characters.—A white, crystalline powder. Inodorous ; taste, faintly bitter. *Solubility.*—In about 170 parts of water, in alcohol (90 p. c.), in solvent ether, in chloroform, and in aqueous solutions of alkali hydroxides and carbonates.
B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

Barbitonum Sodium. (Barbiton. Sod.). **Syn.**—Soluble Barbital ; "Medinal" ; Veronal Sodium.—Barbitone Sodium is obtained by the interaction of barbitone and sodium hydroxide. Contains 98.0 to 101.0 p. c. of $C_8H_{11}O_3N_2Na$.

Characters.—A white, crystalline powder ; odourless ; taste, bitter. *Soluble* in 6 parts of water ; slightly in alcohol (90 p. c.) ; insoluble in solvent ether and in chloroform.
B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

PHENOBARBITONUM. (Phenobarbiton.). **Syn.**—Phenobarbital; "Luminal"; "Gardenal".—Phenobarbitone is obtained by the condensation of ethyl phenylethylmalonate with urea.

Characters.—A white, crystalline powder; odourless; taste, slightly bitter. *Soluble* in 1000 parts of water, in alcohol (90 p. c.), in solvent ether, in chloroform, and in solutions of alkali carbonates and hydroxides.

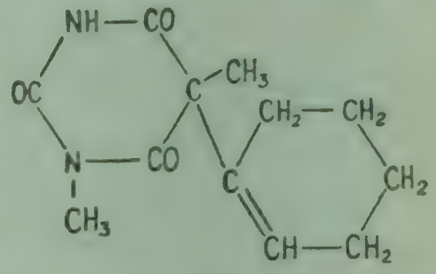
B. P. Dose.—1/2 to 2 grs. or 30 to 120 mg.

Phenobarbitonum Sodium. (Phenobarbiton. Sod.). Syn.—Phenobarbital Sodium; Luminal Sodium.—Phenobarbitone Sodium is obtained by the interaction of phenobarbitone and sodium hydroxide. Contains 98.0 to 101.0 p.c. of $C_{12}H_{11}O_3N_2Na$.

Characters.—A white, hygroscopic powder; odourless; taste, bitter. Very *soluble* in water, soluble in alcohol (90 p. c), insoluble in solvent ether.

B. P. Dose.—1/2 to 2 grs. or 30 to 120 mg. Single dose by intravenous or intramuscular injection:—**1 to 3 grs. or 60 to 200 mg.**

HEXOBARBITONUM. (Hexobarbiton.). $C_{12}H_{16}O_3N_2$. **Syn.**—Hexobarbital; Evipan; Hexobarbitone is 5-Δ^1-*cyclohexenyl*-5-methyl-*N*-methylbarbituric acid.



Characters.—Colourless, prismatic crystals; odourless and tasteless. *Soluble* in about 3000 parts of water at 20°C.; soluble in dehydrated alcohol, in methyl alcohol, in acetone, in benzene, in chloroform and in solvent ether. Soluble in aqueous solutions of the alkali hydroxides, but not in solutions of the alkali carbonates.

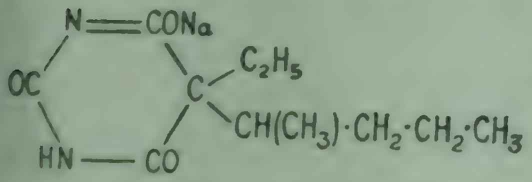
B. P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.

Hexobarbitonum Sodium. (Hexobarbiton. Sod.). **Syn.**—Soluble Hexobarbitone: Evipan Sodium; Cyclonal Sodium.—Sodium Hexobarbitone may be obtained by the interaction of hexobarbitone and sodium hydroxide.

Characters.—A white, very hygroscopic powder; odourless; taste, bitter. Very soluble in water, in alcohol (95 p.c.), in methyl alcohol and acetone. Only slightly soluble in chloroform and in solvent ether; insoluble in benzene. An aqueous solution absorbs carbon dioxide, causing separation of hexobarbitone in crystals.

B. P. Dose.—By intravenous or intramuscular injection.—**3 to 15 grs. or 0.2 to 1 grm.** By rectal injection.—**30 to 60 grs. or 2 to 4 grms.**

PENTOBARBITONUM SODIUM. (Pentobarbiton. Sod.). Syn.—Pentobarbital Sodium; Soluble Pentobarbitone; Nembutal.—It is the mono-sodium derivative of 5-ethyl-5-(1-methylbutyl)-barbituric acid.



Characters.—A white crystalline powder, or granules; odourless; taste, slightly bitter. Very *soluble* in water and alcohol, almost insoluble in solvent ether.

B. P. Dose.—1½ to 3 grs. or 0.1 to 0.2 grm.

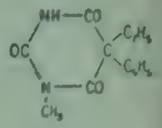
THIOPENTONUM SODIUM. (Thiopent. Sod.). Syn.—Pentothal Sodium.—Thiopentone Sodium is a mixture of 100 parts by weight of mono-sodium derivative of 5-ethyl-5-(1-methylbutyl)-thiobarbituric acid and 6 parts by weight of exsiccated sodium carbonate.

Characters.—A yellowish-white, hygroscopic powder; odour, somewhat alliaceous; taste, bitter. Should be kept in an atmosphere of nitrogen in sealed tubes, and protected from light. *Soluble* in water; partially soluble in alcohol; insoluble in solvent ether.

B. P. Dose.—1½ to 8 grs. or 0.1 to 0.5 grm. By intravenous injection.

METHYLPHENOBARBITONUM. (Methylphenobarbiton.).

Syn.—Prominal ; Phemitonum.—Methylphenobarbitone is *N*-methyl-5-phenyl-5-ethylbarbituric acid.

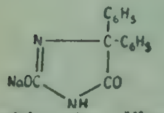


Characters.—A white crystalline powder ; odourless ; tasteless. Almost insoluble in water ; soluble in alcohol (90 p. c.), in solvent ether, in chloroform and in aqueous solution of alkali hydroxides.

B. P. Dose.—1 to 3 grs. or 60 to 200 mg.

PHENYTOINUM SODIUM. (Phenytoin. Sod.).

Syn.—Soluble Phenytoin ; Diphenylhydantoin Sodium ; Dilantin Sodium ; Epanutin ; Solantoin.



Source.—Phenytoin Sodium is the monosodium derivative of 5 : 5-diphenylhydantoin.

Characters.—A white powder ; odourless. Somewhat hygroscopic and on exposure to air gradually absorbs carbon dioxide with the liberation of diphenylhydantoin. Freely *soluble*, in water ; soluble in alcohol (90 p. c.) ; solutions in water are usually somewhat turbid owing to partial hydrolysis.

B. P. Dose.—3/4 to 1½ gr. or 50 to 100 mg.

Official Preparations

1. **Tabellae Barbitoni.—B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.**
2. **Tabellae Barbitoni Sodii.—B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.**
3. **Tabellae Phenobarbitoni.** *Syn.—Phenobarbital Tablets.*—**B. P. Dose.—1/2 to 2 grs. or 30 to 120 mg.**
4. **Tabellae Phenobarbitoni Sodii.** *Syn.—Phenobarbital Sodium Tablets.*—**B. P. Dose.—1/2 to 2 grs. or 30 to 120 mg.**
5. **Injectio Phenobarbitoni Sodii.—B. P. Dose.**—Single dose by intravenous or intramuscular injection :—**1 to 3 grs. or 60 to 200 mg.**
6. **Injectio Hexobarbitoni Sodii.—B. P. Dose.**—By intravenous or intramuscular injection :—**3 to 15 grs. or 0.2 to 1 grm.**
7. **Injectio Thiopentoni Sodii.—B. P. Dose.**—By intravenous injection :—**1½ to 8 grs. or 0.1 to 0.5 grm.**

Non-official Preparations

1. **Nirvanol.**—*Phenyl-ethyl-hydantoin.*—A tasteless, crystalline powder, slightly soluble in water. *Hypnotic* and *sedative.* Useful in *chorea.* Daily dose for a child 9 to 14 years is 5 grs. or 0.3 grm. Treatment is followed, after one to two weeks, by pyrexia and a morbilliform rash, known as "nirvanol sickness" when the treatment should be stopped. There is oedema of the eye lids, conjunctivitis and true eosinophilia. *Dose.*—2½ to 7 grs. or 0.15 to 0.45 grm.

2. **Proponal.**—*Dipropyl-Barbituric Acid.*—A homologue of veronal ; white crystalline powder. Very narrow margin between therapeutic and toxic dose. More toxic than veronal. *Dose.*—2 to 8 grs. or 0.12 to 0.5 grm.

3. **Bromural.** *Syn.—Uvaleral* ; *Dormigene.*—Colourless crystals. Soluble in hot water, ether, alcohol, and the alkalies. Contains 36 p. c. bromine. *Hypnotic* in *neurasthenia. Dose.*—5 to 10 grs. or 0.3 to 0.6 grm.

4. **Amylobarbitonum, B.P.C.** *Syn.—Amytal.—Iso-amyl-ethyl-barbituric acid.*—A white. crystalline powder, with slightly bitter taste. Soluble in alcohol and ether, slightly in water. *Dose.*—As a *sedative*, 1/3 to 3/4 gr. or 20 to 50 mg. (*per os*) ; as a *hypnotic*, 1½ to 5 grs. or 0.1 to 0.3 grm ; as *general anaesthetic*, 3 to 10 grs. or 0.2 to 0.6 grm.

5. **Cyclobarbitonum, B.P.C.** *Syn.—Phanodorm.—Cyclohexenylethyl Barbituric Acid.*—A white, crystalline powder, with a bitter taste. *Dose.*—3 to 6 grs. or 0.2 to 0.4 grm. ; in mild insomnia, 1½ grs. (0.1 grm.).

6. **Theominal.—**A combination of theobromine 0.3 grm. and luminal 0.03 grm. In *arteriosclerosis, angina pectoris,* and other heart affections, and climacteric disorders. *Dose.*—1 to 2 tablets.

7. **Allobarbitone.** *Syn.—Dial* ; *Diallylbarbituric acid.*—A homologue of barbituric acid. *Dose.*—1/2 to 3 grs. or 0.03 to 0.18 grm.

8. **Carbromalum, B.P.C.** *Syn.—Adalin* ; *Uredal.*—A white crystalline powder ; almost odourless and tasteless. *Soluble* in 3000 parts of water. in alcohol (95 p.c.) and in 3 parts of chloroform. *Dose.*—5 to 15 grs. or 0.3 to 1 grm.

9. **Butylethylbarbituric Acid.** *Syn.—Neonal* ; *Soneryl* ; *Butobarbital.*—A white crystalline powder. Soluble 1 in 300 of water. Sedative and hypnotic in insomnia. Produces sleep in half an hour. Is also analgesic. Also used as basal narcotic. *Dose.*—1 to 2 grs. or 0.06 to 0.12 grm.

10 **Somnifaine.—**A compound of diethylamine salts of barbitone with allylisopropylbarbituric acid in water-glycerin-alcohol solution. Used both orally and by injection, which in urgent cases may be given by the intravenous route. Powerful *sedative* and *hypnotic.* Used with success in *mental cases* and in all conditions of excitement. Valuable in convulsive diseases like tetanus, strychnine poisoning, eclampsia, etc. *Dose.*—20 to 40 drops or 8 to 16 ms. (supplied in solution in drop bottles for oral use, to be taken mixed with water). For intramuscular injection, 2 mils or one ampoule.

11. **Thialbarbitone.** *Syn.*—*Kemithal.*—It is Sodium cyclohexenylallylthiobarbiturate. Action similar to pentothal sodium but half as potent. Respiratory depression is less. Used intravenously to produce general anaesthesia. 5 to 10 p.c. solution as a preanaesthetic.

PHARMACOLOGY OF BARBITURATES

Central nervous system.—All the different derivatives of this group depress the cerebrospinal axis and have practically the same action, *viz.*, **hypnotic, analgesic** and **sedative**, but differ only in degree and duration, and this depends partly upon the rate of excretion and partly upon the rate of destruction of the drug. The intensity of their action can be modified with the amount used and will produce sleep, complete insensibility or coma according to the dose. Since barbituric acid is unstable and does not possess any narcotic action these drugs are rendered useless by the oxidation of their side-chains, and the compounds with unstable side-chains produce very short action. They all belong to the *aliphatic series*, and as such their action varies with their solubility in fats.

As *hypnotics* they produce refreshing sleep with adequate oral dose lasting for 6 to 8 hours without any unpleasant after-effects. They take about half an hour or more to produce sleep by their éffects entirely on the central nervous system. They are about twice as active as chloral and four times as strong as sulphonal. Sometimes sleep is preceded by excitement and delirium.

As *analgesics* they are inferior to opium alkaloids and drugs of the antipyretic group and do not relieve pain without loss of consciousness. Therefore these drugs will not produce sleep in the presence of pain. As *sedatives* they all relieve convulsion. Barbitone is a sedative and hypnotic ; phenobarbitone, amytal and pernocton are more analgesic and less hypnotic, depress the motor area, and are slightly more toxic. Phemitone and dilantin are more sedative and better anticonvulsants.

In sufficient doses they produce surgical anaesthesia, specially when administered intravenously. The patient suddenly falls asleep and the different stages observed in volatile anaesthesia are not elicited, except when injection is given very slowly.

Respiration and circulation.—No effect is observed on respiration, except some slowing, which is not more than found in natural sleep. Toxic doses depress the respiratory centre, when breathing becomes slower, shallower and even irregular. Death takes place from pulmonary oedema and paralysis of the centre.

Ordinary hypnotic doses have no effect on circulation. The blood pressure remains normal though the heart may be a little quickened. Given intravenously, as for the production of anaesthesia, both the heart and the blood pres-

sure may be depressed, but the pressure returns to normal soon.

Temperature.—Barbiturates diminish to some extent the basal metabolic rate. Sedative doses lower the temperature slightly, which becomes very low in coma due to depression of the medullary centres and also from lessened movements.

Smooth muscles.—All depress the smooth muscles producing loss of tone, specially of the uterus. Amytal however has very little effect on the normal uterine contractions and in anaesthesia produced by amytal the uterine contractions continue.

Margin of safety.—Since these drugs are extensively used as hypnotics and analgesics it is necessary that the margin of safety between the hypnotic dose and the lethal one represented by the ratio $\dfrac{\text{minimum lethal dose}}{\text{minimum therapeutic dose}}$ should be known. The higher this figure the safer the drug. Luminal is 1.3 ; barbitone, 1.6 ; soneryl, nembutal and phanodorm, 2.4 ; dial, 2.5 ; evipan, 5. Thus it is not very safe to give luminal in full hypnotic doses, although in sedative antiepileptic dosage it is free from immediate risk.

Absorption and clearance.—These drugs are quickly absorbed and are either destroyed by the liver or excreted by the urine. Under normal conditions they do not interfere with renal functions. The secretion of urine may be diminished either from central effect, or on the hypothalamic-pituitary system, or through depressed circulation. Barbitone passes out of the body in most part unchanged, about 70 p.c. being found in the urine, and takes several days to eliminate even after a single dose. Its use should not therefore be continued for more than one week, otherwise symptoms of poisoning may develop. 65 p.c. of pernocton, 30 p.c. of dial, between 10 and 40 p.c. of luminal, and no amytal could be recovered from the urine. Amytal, nembutal and evipan with unstable side chains are metabolised completely in a few hours. Traces have been found in the cerebro-spinal fluid and milk.

They undergo destruction in the liver, and on this depends the explanation of the evanescent effect of the short-acting compounds ; whereas patients with damaged liver do not detoxicate it and may therefore remain under its effect for a longer period. The portion which escapes detoxication is eliminated in the urine, but its excretion is slow, and this accounts for the longer duration of the action. After large doses traces have been found in the milk.

For practical purposes the barbiturates are classified according to their rate of clearance as follows :

1. *Slow clearance group.*—These are mostly excreted by the urine and undergo little or no decomposition in the tissues. As much as 85 p.c. of these compounds may be recovered from the urine. Consequently their action is prolonged and an ordinary hypnotic dose may leave the patient sleepy the following day. These are not used for premedication or for production of general anaesthesia. They are barbitone, phenobarbitone, butobarbitone and dial.

2. *Rapid clearance group.*—These are detoxicated in the liver so that very little can be recovered in the urine. Even when used in large doses they are cleared in from four to six hours. They are valuable as hypnotics and for premedication. Compounds of this group are, cyclobarbitone, amytal, pentobarbitone (nembutal). They are also valuable as anticonvulsant.

3. *Very rapid clearance group.*—These compounds are very rapidly cleared from the system and are used intravenously for the production of general anaesthesia. They are hexobarbitone sodium and thiopentone sodium.

Idiosyncrasy.—In about three per cent. of cases idiosyncrasy to barbiturates is observed and toxic symptoms may arise even after administration of very small doses. They may take the following forms:—

1. *Skin.*—Urticarial rashes, bullae, morbilliform or scarlatiniform maculo-papular erythema.

2. *Gastro-intestinal.*—Anorexia, nausea, epigastric pain, diarrhoea.

3. *Nervous.*—Defects of attention and memory, lassitude, fatigue and backache, confusion, delusions and hallucinations, diplopia, nystagmus and even coma.

4. *Circulatory.*—Most barbiturates are cardiac depressants of more or less serious nature, and all cause some fall of blood pressure.*

Antagonism and Synergism.—Barbiturates are antagonistic to strychnine, cocaine and similarly acting drugs and have been used successfully in poisoning by these drugs. Thus the lethal dose of strychnine may be increased several times by the previous administration of barbiturates. While recognising the stimulating effect of caffeine and ephedrine in barbiturate narcosis, the 'awakening' effect of picrotoxin, leptazol and nikethamide in these conditions has also been demonstrated. In fact the relative value of the different *analeptics* has been studied on the basis of this observation. They depress the hypothalamic centres which control the autonomic activities and therefore liable to affect the autonomic system. Thus, amytal reverses the excitor effect of the vagus, and phenobarbitone reverses the inhibitory effect of the sympathetic, on the stomach.

Toxicology.—The action of these derivatives varies in different individuals. While symptoms of poisoning have been reported with 1 gr. of veronal, recovery has also taken place even after 60 grs. All these drugs are more or less cumulative and the symptoms of overdosage are often due to this factor, *i.e.* when continued for long

* Castleden : *The Practitioner*, Sept., 1936.

even in therapeutic doses, but are specially common when excretion is also scanty due to the kidneys not functioning properly. A case of delusional insanity following nembutal-ether anaesthesia occurred after 3 grs. (two capsules) of nembutal with 1/100 gr. of atropine by the mouth before administration of gas-ether anaesthesia.*

When a toxic dose is taken headache, vertigo and ataxia would appear in a few minutes, and there may be a short period of excitement. The patient would fall asleep and then pass on to coma. Babinski's reflex may be positive for a time, but soon all reflexes and sensations are lost. Cyanosis is as a rule present with stertorous and irregular breathing which may stop for a while in the later stages. Temperature becomes subnormal, pulse rapid. Retention of urine is common. First catheter specimen contains large amount of the drug. Coma may last for several days.

Treatment.—If seen within four hours, repeated washing of the stomach with warm water. No alkalies should be given as they combine with the drug to form soluble salt which is very quickly absorbed. Put 1 pt. of strong hot coffee with some milk and 1 oz. of castor oil. If seen after six hours, lavage is still useful. In fact lavage should be repeated twice after interval of four hours. Colon should be washed out at once and again after 12 hours. Strychnine 1/8 gr., picrotoxin 1/12 to 1/6 gr., leptazol and nikethamide, and atropine 1/100 gr. every four hours, or ephedrine 1½ grs. Subcutaneous injection of warm saline solution and rectal use of saline and glucose 5 p.c. Oxygen if cyanosis is present. Hasten removal of the poison from the central nervous system specially from the vital medullary centres by lumbar puncture at once and repeated every 12 to 24 hours which helps to reduce cerebrospinal pressure and elimination of the poison.

Fatal Dose :—Death has been caused by 15 grs. of luminal and of veronal ; 28 grs. of dial ; and 6 grs. of nembutal used for premedication in hyperthyroidism. Average fatal dose is larger ; 50 grs. for veronal and 30 grs. of luminal should be considered fatal.‡

Therapeutics of Barbiturates

The chief uses of the different preparations of this group are as hypnotics, sedatives, analgesics and anaesthetics.

As *hypnotics* these derivatives have come to the forefront and are used in preference to the sulphonal group because of their liability to poisonous effects and paraldehyde which is disagreeable. They produce almost natural sleep within 20 to 30 minutes lasting for 6 to 8 hours from which the patient wakes up refreshed, although some lassitude remains during the day. They can be used in any form of insomnia and are of extreme value when sleeplessness is due to nervous excitability, mental disease and cerebral excitement. As hypnotics, barbitone and soluble barbitone are given in 7½ gr. and phenobarbitone and amytal in 1½ gr. doses. As hexobarbitone is rapidly excreted its hypnotic effect is of short duration. Luminal sodium being soluble in water can also be given hypodermically. Soneryl is an analgesic and hypnotic. Therapeutic doses produce no untoward effect on circulation and respiration, nor

* *Royal Society of Medicine, Aug.,* 1932.

‡E. Roche Lyneh : *British Meidcal Journal, December.* 5, 1936.

damage the kidneys. It produces sleep within half an hour **and does not produce a habit.**

They are valuable *sedatives* to the brain and as such are more prompt than bromides and can be used in all cases where bromides are indicated. Luminal is also useful in vomiting of pregnancy and sea-sickness in doses of 0.06 to 0.12 grm. (1 to 2 grs.) half an hour before meals. Alone or combined with belladonna it is useful in pyloric stenosis and colic. Because they have greater power to allay motor excitability, phenobarbitone, soluble phenobarbitone, methylphenobarbitone (phemitone) and phenytoin sodium (dilantin) are used in various **convulsive diseases**, e.g. in mania, delirium tremens, excitement following the withdrawal of morphine, epilepsy, strychnine poisoning and in tetanus. But their greatest field of usefulness is in **epilepsy in which disease they have almost replaced bromides**, although in some persons an effective dose causes drowsiness and difficulty in concentration. In **epilepsy** phenobarbitone is more valuable in acute attacks and reduces both the number and severity of the fits, and does not produce that mental hebetude so common after prolonged use of bromides. The best method of administration is to prescribe 1½ to 2 grs. twice a day, or in nocturnal attacks only one dose just before going to bed. The dose requires to be regulated, keeping in mind the idiosyncrasy of the patient and the liability of the drug to produce skin rash. The object being to control the attacks without producing any toxic effects. Many patients however will tolerate 3 gr. (0.2 grm.) daily without any unpleasant symptoms. It is not a cure for epilepsy and requires to be continued for a long time, possibly for years, and the dose gradually reduced. If no change is observed at the end of six months the treatment should be stopped. Methylphenobarbitone (phemitone) is more effective in severe cases than phenobarbitone. It is also useful in **whooping cough.** Phenytoin sodium is also used in epilepsy, particularly in patients who fail to respond under phenobarbitone and bromides. It is specially effective in *grand mal* than in *petit mal.* It does not possess the sedative effect of phenobarbitone and appears rather to inhibit the epileptic discharge than protect the brain from its effects. With its use the attacks may be fewer but more severe when they do occur. It has therefore been suggested that a combination with phenobarbitone is desirable. The change should be made gradually with overlapping of dosage ; too rapid withdrawal from luminal or bromide may increase the frequency of seizures. It however may cause a variety of toxic reactions, like nausea, dizziness or skin rashes, which disappear on reduction of the dose ; while exfolia-

tive dermatitis and purpura are of a more serious natur and require stoppage of the drug. The dose for adult $1\frac{1}{2}$ grs. (0.1 grm.) three times a day, increased if nece sary to maximum of 3 grs. (0.2 grm.).

As *analgesics* they are useful in headaches of all kind and are valuable in reducing pains of a **neuralgic** natu *e.g.* sciatica, intercostal neuralgia, lumbago, dysmeno rhoea, etc. They are often used in combination wi amidopyrine derivatives, *e.g.* Allonal and Veramo When thus combined the stimulating effect of amidopyri is neutralised by barbitone, and the depressant action the latter is delayed and diminished by the former, ar that each raises the lethal dose of the other. Other ant pyretics and acid acetylsalicylic also behave similarly.

As *anaesthetics* they have been used either for th production of general anaesthesia or as a preliminary the use of volatile anaesthetics. Their use as a gener anaesthetic is open to many objections. Being no volatile they cannot be given by inhalation and therefo the dose cannot be regulated. If, for instance, a small do has been given it can always be increased, but if a larg dose has been introduced it cannot be withdrawn ; wher as the dose of volatile anaesthetics can be regulated will according to the need of the patient. Further, owin to their slow excretion the narcotic effect lasts for man hours, often with injurious effect to the patient. The use therefore has not been generally accepted by many com petent authorities and the mortality following their us was greater than with volatile anaesthetics. Moreove the intravenous injections require large amounts of alka for solution and when they enter the blood they are pr cipitated and remain as foreign bodies in a colloidal stat thus altering the colloidal equilibrium of the blood whic may give rise to certain "reflex" effects. On the other han for the production of **basal narcosis**, as a preliminary volatile anaesthetics, they are largely used. (*See* page 16

All these different drugs are not suitable for admini tration by one route. Hexobarbitone sodium and sodiu thiopentone if given intramuscularly, cause severe loc reaction, they are *par excellence* intravenous anaestheti Thiopentone sodium produces better muscular relaxati and has slightly prolonged action than hexobarbito They are all detoxicated by the liver and the oxidised pr ducts are excreted by the kidneys.

The different barbiturates vary in their power of toxication and elimination (*see* page 206). If the proper of speedy detoxication runs side by side with a wi margin of safety the drug is suitable for intravenous u in sufficient amount to produce complete narcosis and mu cular relaxation. The rectal, oral, or the intramuscu

…ate is employed for the slowly detoxicated drugs. There …re however certain possible dangers which should be re…membered, *viz.*, (1) *idiosyncrasies* to the drug; (2) *inabi…ty on the part of the body to detoxicate the drug*, as …appens to patients with bad liver; (3) *combination of …veral narcotics*, e.g. morphine is specially dangerous and …ay depress the respiration profoundly.

Administration.—Barbiturates may be administered by the fol…wing routes : 1. *Oral.*—It is the best, simple and safe and should … employed whenever possible. All barbiturates are absorbed …tisfactorily from the intestinal tract.

2. *Rectal.*—It is useful for infants or in severe vomiting. It …ay be administered either as a suppository or as retention enema … a soluble salt.

3. *Subcutaneous or intramuscular.*—When rapid sedative or …ypnotic effect is required as in convulsive diseases.

4. *Intravenous.*—This route should only be used in emergencies for production of basal anaesthesia.

Caution.—The use of barbiturates is not always unattended with …quelae. Sometimes the patient will sleep deeply, for a period …fficiently long to cause anxiety. A minor but troublesome com…ication is restlessness preceding return to full consciousness. This …owever is less with nembutal than with others. All basal narcotics …use depression of the respiratory centre, so that in some cases the …eathing becomes so quiet and shallow that the patient scarcely …kes sufficient anaesthetic to secure surgical anaesthesia. Cyanosis … also another complication. Toxic condition and hyperthyroidism …crease the sensitiveness to these derivatives, 6 grs. of nembutal …oved fatal in Graves' disease. They should not be used in those …o have a special idiosyncrasy to the drugs or in those with im…ired renal or hepatic function. Untoward symptoms are more …ely to occur in patients suffering from fever, diabetes, severe …aemia and congestive heart failure. Owing to their depressant …fect on the central nervous system all barbiturates should be used …th caution to the very young and the old and enfeebled patients.

Quinalbarbitone Sodium. (Not official). **Syn.**—Seconal Sodium. It is a monosodium derivative of 5-allyl-5-(1-methylbutyl) barbi…ric acid. It belongs to the rapid clearance group of bartiturates …th action almost similar to pentobarbitone except that its duration … effect is shorter. It is a better *hypnotic* since there is less ten…ncy to sleepiness the day after administration. It is also used as *…preanaesthetic* prior to general anaesthesia. As an *anticonvul…nt* it is employed in the treatment of strychnine poisoning, tetanus …d status epilepticus.

Dose.—*As hypnotic*, 0.1 to 0.2 grm. ($1\frac{1}{2}$ to 3 grs.) ; as *preanaes…etic*, **0.2 to 0.3 grm. (3 to 5 grs.)**

URETHANUM

$$(\text{Urethan.}).\ OC < {NH_2 \atop OC_2H_5}$$

Source.—Urethane is ethyl carbamate, and may be prepared by … action of ammonia on ethyl chloroformate.

Characters.—Colourless, prismatic crystals or leaflet. Odourless ; taste, cooling, … and slightly bitter. Soluble in 2 parts of water, in 1 part of alcohol (95 p. c.), … solvent ether, chloroform, glycerin and fixed oil.

B. P. Dose.—15 to 30 grs. or 1 to 2 grms.

Official Preparation

1. *Injectio Quininae et Urethani.* Quinine hydrochlor. 12.5 p.c. and urethane

6.25 p. c. **B. P. Dose.—8 to 75 ms. or 0.5 to 5 mils.** By intravenous injection sclerosing agent.

PHARMACOLOGY AND THERAPEUTICS

Urethane is a safe hypnotic in doses of 20 to 30 g but is weak and less certain. At first it produces some citement, but this is quickly followed by natural sleep w some slowing of respiration and the pulse. Bl pressure is not lowered, but large doses lower temperature and weaken and even abolish the reflexes. does not relieve pain. It is specially suitable for childr cases of delirium tremens, acute mania, and in the inso nia of heart disease. It is **antagonistic to strychnine** a has proved more useful than chloral in tetanus. It is o dised in the body into urea and therefore acts as a *diure* Combined with quinine hydrochloride it is used in treatment of varicose veins as Inj. Quininae et Uretha

Urethane has been used with promising results **leukaemia** in 15 gr. (1 grm.) doses given three or f times daily when it causes a fall of white cell count in th to four weeks. The response in lymphatic variety is l satisfactory than in myeloid leukaemia. The leucoc count falls within normal limits, the spleen and enlarged lymphatic glands diminish in size and there i rise of haemoglobin level and red cells. Favourable resu followed its use in **multiple myeloma.** It may also be u intramuscularly or intravenously. It is relatively n toxic and should be used continuously and the maintena dose regulated by clinical trial. Over-dosage may ca dangerous fall of both white and red cells.

3. INORGANIC HYPNOTICS

POTASSII BROMIDUM

Potassium Bromide. (Pot. Brom.)

Source.—Obtained by the interaction of ferrous bromide v potassium carbonate. Contains not less than 98.5 p.c. of pure po sium bromide.

Characters.—In colourless, transparent or opaque, crystals, or a white gra powder ; taste, saline. *Solubility.*—1 in 2 of water, 1 in 200 of alcohol (90 p

Incompatibles.—Solution containing free chlorine or free acids, spiri nitrous ether if acid, mercury, silver salts, and strychnine.

B. P. Dose.—5 to 20 grs. or 0.3 to 1.2 grms.

OFFICIAL PREPARATION

1. **Tabellae Potassii Bromidi.—B. P. Dose.—5 to 20 grs. or 0.3 to 1.2 g** When the quantity to be contained in a tablet is not mentioned, 5 gr. tablets s be supplied.

SODII BROMIDUM. (Sod. Brom.).—Contains not less than p.c. of pure sodium bromide.

Characters.—Small, colourless, transparent or opaque cubical crystals, white granular powder, deliquescent, inodorous ; taste, saline. *Solubility.*— 1.5 of water, 1 in 16 of alcohol (90 p. c.).

B. P. Dose.—5 to 20 grs. or 0.3 to 1.2 grms.

NON-OFFICIAL PREPARATIONS

1. **Ammonii Bromidum, B.P.C.**—In small colourless crystals ; saline pu taste. Soluble in water. *Dose.*—5 to 30 grs. or 0.3 2 grms.

. Liq. Bromidi Compositus. B. P. C. *Syn.—Bromidia.*—1 dr. contains 15 grs. each of Chloral Hydrate and Pot. Bromide with Extract of Cannabis Ind. —1/2 to 2 drs. or 2 to 8 mils.

. Bromoformum. B.P.C.—It is tribromomethane. Contains about 4 p.c. A colourless, volatile, sweet liquid, with an agreeable odour. Soluble in ...form, ether, and slightly in water. In *whooping cough. Dose.*—1/2 to 2 ms. ... to 0.12 mil.

. Acidum Hydrobromicum Dil., B.P.C.—A clear, colourless, odourless liquid. —15 to 60 ms. or 1 to 4 mils.

Pharmacology of Bromides

Internally. **Alimentary canal.**—Either in concen-ated solution applied to the throat or in repeated large oses given by the mouth, bromides diminish the sensi-lity and the reflex excitability of the fauces. The bromides re readily absorbed by the gastro-intestinal mucous mem-rane and circulate as sodium bromide. Large doses in ncentrated solutions produce nausea, vomiting and gas-ralgia by their local salt action.

Heart and circulation.—In therapeutic doses there is o essential effect on the heart and circulation, but in car-ac neuroses the bromides make the heart slow, steady nd quiet through their general sedative effect. It is only hen potassium bromide is used intravenously that the eart is depressed like other potassium salts.

Respiration is only slightly depressed and becomes lower. This however is not more than is observed in atural sleep. The coughing reflex is diminished.

Nervous system.—The chief action of bromides is on he entire nervous system, which is **moderately depressed** nd owing to slow excretion this depression can be main-ained for a long period without any effect on the vital cen-res or the medulla. This fact makes it so valuable in the reatment of epilepsy where it is necessary to keep the entral nervous system depressed for a prolonged period. sed for long, even in small doses, bromides make the atient dull and apathetic with impairment of the power f concentration. They **lessen the functional activity of he brain.** The sensibility, excitability and emotional ctivity are all diminished, thereby inducing a state most avourable for sleep. They cause sleep by rendering the rain less sensitive to external influences. The sleep is ot always refreshing and owing to the slow excretion is ollowed by drowsiness and weariness. Since the sensory rea is not depressed bromides do not relieve pain. They epress the motor area and block the passage of sensory mpulses along paths which connect the motor cells of the ord, while the connections between cerebral centres and he motor cells of the cord remain intact. Cutaneous sen-ation is also impaired by comparatively small doses, not rom any peripheral action but from central effect.

The vital centres are more or less depressed by large oses, and there is considerable impairment of the reflex

excitability, so that larger doses of strychnine than usu are required to elicit convulsion. They diminish the ir tability of the mucous membranes, the earliest and mo marked being the throat which can be touched and ex mined without inducing reflex vomiting, although sens tion of touch remains unimpaired. After larger dos complete anaesthesia may be induced.

Muscles.—The bromides not only impair the activi of the muscles by their action on the motor-cells and refl centres, but by their direct influence on the muscles them selves. They may be paralysed to such an extent that convulsions can be produced by poisoning with strychnin Therefore they are powerful **anticonvulsants.**

Genitals.—Bromides decidedly lessen virility and, continued long, the sexual passion, due either to its acti on the brain, or diminished reflex activity.

Elimination.—Inspite of the fact that elimination bromide by the kidneys begins soon after administratio the process is slow and traces have been found 20 da after cessation of administration. Owing to this fact ce tain saturation of the organism results. During a lo course of bromide treatment the blood always contai bromides and the chlorides are correspondingly diminishe They also partially replace chlorides in other tissu accumulating in the largest amounts in those organs whi normally are richest in chlorine. For instance, hydrobr mic acid appears in gastric juice. The elimination of br mides depends upon the amount of sodium chloride intak the rate being increased by it. Conversely a salt-free di retards their excretion and helps saturation in the bod The rate of substitution depends upon the amount of br mide given, quantity of fluid and chloride intake and t efficiency of the kidneys of the patient.

As the salt intake varies in different individuals, follows that the amount of bromide remaining in the bo after a standard dose will also vary. Thus if 30 grs. bromide be given to a person who is on a low salt diet a has a small fluid intake, bromide concentration in the blo after 24 hours will be higher than when the same amou is given to a patient who is on a normal diet. This e plains why some patients taking say 10 grs. three tim a day develop toxic symptoms after a few weeks, wh others can take the same amount for a much longer peri without showing any untoward symptoms.

Bromides are eliminated by the intestinal and bro chial mucous membrane, skin, saliva and milk.

Acute toxic action.—Acute poisoning is rare, but if half to o ounce is swallowed, weakness, frontal headache, reduction of pu rate, insensibility, aphasia, amnesia are the chief symptoms. I covery as a rule takes place unless oedema of the lungs supervene

Barbour *et al.** have pointed out that the use of bromides in large doses is followed by symptoms of bromide intoxication even in the absence of so-called bromide rash. Normally the concentration of bromide in the blood is 0.5-2.5 mg. per cent. but the concentration may be as much as 500 mg. per cent. in fatal intoxication. The toxic threshold may be taken as 300 mg. per cent. Elderly patients and those suffering from arterio-sclerosis, anaemia, renal inefficiency or organic heart disease show symptoms of toxicity early and the toxic threshold with these people is in the region of 150 mg. per cent.

The symptoms of intoxication are insomnia, delirium, confusion, hallucination with varying degrees of disorientation, hysterical manifestations with torpor and death. The common physical signs are dry skin, furred tongue, tremors, blurred speech and unsteady gait.

Chronic toxic action or "Bromism."—The symptoms of chronic poisoning are observed after prolonged use of bromides, as happens in the treatment of epilepsy. The earliest of them is a rash resembling acne, which appears mostly on the face and back and sometimes may lead to boils. Mental dullness, anaemia, muscular weakness, general prostration, and dulling of cutaneous sensibility and that of the pharynx. These are followed by diminution of sexual power, and a general lowering of vitality and vigour.

In some the symptoms are more of the *psychotic type*. There may be restlessness, hallucination and delusion, disorientation and a sense of persecution. In severe cases respiration becomes depressed, slow and laboured, pulse feeble and eventually fever comes in followed by death.

Treatment.—As a rule stoppage of the drug is sufficient in the early stage. Administration of sodium chloride helps elimination and should be given either by the mouth in 15 gr. doses three times a day, or in urgent cases, physiological saline solution intravenously (100 to 400 mils or 3 to 12 ozs.) daily. Caffeine and strychnine should be given to counteract depression.

Therapeutics of Bromides

Internally.—Bromides are chiefly used therapeutically as **sedatives** in hypersensitive state of the nervous system. They are also used as **hypnotics** to promote sleep, but are not of value when sleeplessness is due to painful conditions. Bromides may be therapeutically used :—

1. As a *hypnotic* in sleeplessness caused by worry, overwork or mental strain ; but they are of no use when sleeplessness is due to pain. Sometimes however bromides fail to produce sleep and give rise to much depression and confusion. In delirium tremens, mania, acute inflammatory and febrile diseases, cerebral congestion, night screaming of children, nightmare of children and adults, bromides may be used with the greatest benefit either to induce sleep or to allay irritability. It is often combined with chloral hydrate.†

2. *To allay slight pain* which is keenly felt on account of the hypersensitiveness of the nervous system.

* *British Medical Journal, Nov. 14, 1936.*

† Pot. brom.
Chloral hydr. aa grs. 15
Syr. aurant. ms. 30
Aqua chlorof. ad. oz. 1
As a hypnotic and in convulsions.

3. *To lessen excitability* in irritability of temper, nervous excitability of women either during the latter months of pregnancy or the change of life, hysteria, hypochondriasis, etc.*

4. *To prevent convulsions* they are used in infantile convulsions, epilepsy, puerperal eclampsia, hysteria, chorea, tetanus and strychnine poisoning. In epilepsy their efficacy is more marked in *grand mal*, producing little or no effect in *petit mal*. In this disease large doses are required if any physiological effects are to be obtained, and must be continued for prolonged periods. No definite results are obtained until the body is saturated with bromide, and this is helped by keeping the patient on a salt-free diet. The regulation of the dose is an important factor. Commencing with a dose of 10-15 grs. given three times a day it should be slowly increased till the maximum is reached, as judged by the patient's condition, *i.e.* cessation of fits. This dose should be maintained for some time and then reduced in the same manner. The treatment should be continued as long as necessary, the aim being to find out the optimum dose that will keep away the fits. A few patients do not show any improvement, and in some the fits return with the stoppage of treatment. It should be noted that although other compounds may contain bromine, e.g. bromoform, they are not of any value in epilepsy since they do not liberate bromine ion in the body. Its use has been greatly replaced by methylphenobarbitone (phemitone), phenobarbitone (luminal), phenytoin sodium (dilantin), troxidone (tridione) and methoin (mesontoin).

5. *To lessen sexual excitability*, as in chordee and nymphomania.

6. As a *sedative in all spasmodic conditions*, such as pertussis, asthma, hiccough, laryngismus stridulus, etc.

7. As a *cardiac sedative* in nervous arrhythmias.

8. *To check reflex or central vomiting*, as sea sickness, etc.

Potassium bromide and dilute hydrobromic acid lessen the disagreeable effects of quinine. The usual practice is to order 2 ms. of the acid for every grain of quinine. Bromide rash is checked by keeping the skin clean and using small doses of arsenic.

Prescribing hints.—Bromides may be administered by the mouth or rectum. Their taste is fairly well disguised by the liquid extract of liquorice, milk or beer. For an enema they may be dissolved in gruel or mucilage. Their efficacy is greatly enhanced if the patient is restricted to vegetable food and a salt-free diet. The hypnotic effect of the bromides may be greatly increased if they are given

* Pot. brom.	grs. 10-15
Tinct. valer. ammon.	ms. 30
Sp. ether. co.	ms. 15
Tinct. asafoet.	ms. 30
Aqua camphor.	ad. oz. 1

with chloral hydrate, morphine or hyoscyamus. Anaemic persons cannot bear a protracted course of bromide treatment. Children, even very young ones, bear bromides well. Bromides should not be prescribed with strychnine or other alkaloids in a mixture, as they throw down alkaloidal precipitates, especially if the solution is concentrated. They should not be prescribed with mineral acids which decompose it, bromine being liberated. With organic acids no such effect is produced as bromine is less easily formed than chlorine.

CLASS B : Drugs acting on the Medulla

Medulla oblongata is an important part of the brain because many vital centres are located there. They are chiefly the respiratory, vagal, vaso-motor, cough and vomiting centres. All drugs which stimulate the central nervous system also stimulate the medulla and the cardiac centre, but the vagal effect predominates. The result of stimulation of the medulla is slowing of the rate of the heart, rise of blood pressure and increased respiration.

The medullary centres are controlled by centres in the hypothalamus which also control the sympathetic and parasympathetic systems, and also emotion. The hypothalamic region regulates the water, salt and carbohydrate metabolism. The sleep centre is also situated in the hypothalamus. There exists a close relationship between the hypothalamus and posterior pituitary, one being interdependent on the other.

The medulla may be stimulated directly by leptazol, nikethamide, camphor, picrotoxin, strychnine, caffeine, ephedrine, lobeline and CO_2 ; and reflexly from some peripheral stimulation, as for instance, by mild electric shock, counter-irritants, and through irritation of the nose, throat and the stomach. All drugs however do not equally affect all the centres, *e.g.* morphine stimulates some and depresses others ; while strychnine, atropine, caffeine, etc., possess other important actions besides being medullary stimulants.

A particular group of drugs produce their main action on the medulla. They stimulate the respiratory centre and tend to raise the blood pressure by acting on the vaso-motor centre, and often help to revive a patient when these show signs of failure, and are classed as **analeptics.** In large doses they produce co-ordinated convulsions of clonic type, *i.e.* different from those produced by strychnine, which are tonic. Apart from the drugs of this group which act as analeptics by acting on the medullary centres, ephedrine, methedrine and pholedrine are also used as analeptics, but these produce their effect by acting on the heart and blood-vessels.

Drugs acting on the medullary centres may be classified as follows :—

I. Drugs acting on the Respiratory Centre

(a) Drugs which directly stimulate the respiratory centre :

Leptazol, Nikethamide, Picrotoxin, Camphor, Atropine, Caffeine, Lobeline, Ephedrine, Strychnine, Cocaine and Carbon Dioxide.

The centre is stimulated reflexly by carbon dioxide through sino-aortic chemo-receptors ; from stimulation of the skin either by application of cold or heat and counter-irritants ; inhalation of ammonia ; and fall of blood pressure.

(*b*) *Drugs which depress the respiratory centre* : Morphine, Heroine, General Anaesthetics, Narcotics, Barbiturates, Chloral Hydrate, Aconite, Hydrocyanic Acid.

II. Drugs acting on the Vaso-motor Centre

(*a*) *Drugs which directly stimulate the vaso-motor centre* : Leptazol, Nikethamide, Picrotoxin, Camphor, Caffeine, Atropine, Carbon Dioxide, Digitalis group of drugs and Cocaine.

The vaso-motor centre is stimulated reflexly from the stomach by alcohol and volatile oils generally, and from the skin by counter-irritants.

(*b*) *Drugs which depress the vaso-motor centre* : Narcotics and General Anaesthetics, large doses of Alcohol, Hydrocyanic Acid and Antipyretics.

III. Drugs acting on the Vagal Centre

(*a*) *Drugs which directly stimulate the vagal centre* : Digitalis group of drugs, Strychnine, Caffeine, Camphor, Morphine, Atropine (early effect) and Aconite.

The vagal centre is stimulated directly by increased carbon dioxide tension and increased chloroform tension in the blood ; and reflexly by high blood pressure, which distend the carotid sinus, and by stimulation of the sensory nerve-endings of the fifth and tenth nerves.

(*b*) *Drugs which depress the vagal centre* : Narcotics and General Anaesthetics (later stage).

IV. Drugs acting on the Vomiting Centre, *see* Emetics.

V. Drugs acting on the Cough Centre, *see* Expectorants.

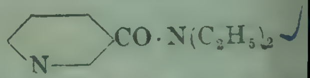
ANALEPTICS

Nikethamide, Leptazol, Picrotoxin, Camphor (q. v.), **Ephedrine** (q. v.), **Methedrine** (q. v.), **Pholedrine** (q. v.), **Caffeine** (q. v.).

NIKETHAMIDUM

(Nikethamid.)

Syn.—Coramine ; Anacardone ; Corvotone ; Cardiamid.



Source.—Nikethamide is the diethylamide of pyridine-β-carboxylic acid, and may be prepared by the action of thionyl chloride on nicotinic acid, and treatment of the resulting acid chloride with diethylamine.

Characters.—A colourless or yellowish oily liquid, or crystalline solid ; almost odourless ; taste, faintly bitter, followed by a faint sensation of warmth. Miscible in all proportions with water ; readily soluble in alcohol (90 p. c.), in solvent ether, in chloroform and in acetone.

B. P. Dose.—5 to 15 grs. or 0.3 to 1 grm. By subcutaneous, intramuscular or intravenous injection.—**4 to 15 grs. or 0.25 to 1 grm.**

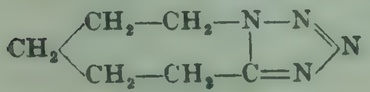
OFFICIAL PREPARATION

1. **Injectio Nikethamidi.**—Strength 25 p. c. **B. P. Dose.**—By subcutaneous, intramuscular or intravenous injection.—**15 to 60 ms. or 1 to 4 mils.** Contains 15 grs. in 60 ms.

LEPTAZOLUM

(Leptazol.)

Syn.—Metrazol ; Cardiazol ; Cartazol ; Corasol.



Source.—Leptazol is pentamethylenetetrazole, and may be prepared by the interaction, in cold benzene solution, of hydrazoic acid and cyclohexanone.

Characters.—Colourless crystals, or a white crystalline powder ; odourless ; taste slightly pungent, bitter. Readily soluble in water, in alcohol (95 p.c.), in solvent ether and in chloroform.

B. P. Dose.—3/4 to 1½ grs. or 50 to 100 mg.

OFFICIAL PREPARATION

1. Injectio Leptazoli.—Leptazol 10 p. c. 1½ gr. in 15 ms. **B. P. Dose.—By subcutaneous injection.—8 to 15 ms. or 0.5 to 1 mil.**

PHARMACOLOGY OF NIKETHAMIDE AND LEPTAZOL

Alimentary canal.—Administered by the mouth both leptazol and nikethamide are absorbed from the alimentary canal and produce systemic effects, leptazol acting more rapidly than nikethamide. Typical action is observed when administered parenterally.

Central nervous system.—Both the drugs are powerful stimulants to the central nervous system, and in large doses cause increased excitability and irritability with tremors and muscular twitchings, followed by convulsions of varying intensity depending upon the dose. Leptazol is more powerful than nikethamide. The **medullary centres** are powerfully **stimulated**, chiefly the respiratory and the vaso-motor centres. Leptazol also stimulates the vomiting centre and acts as a **central emetic.**

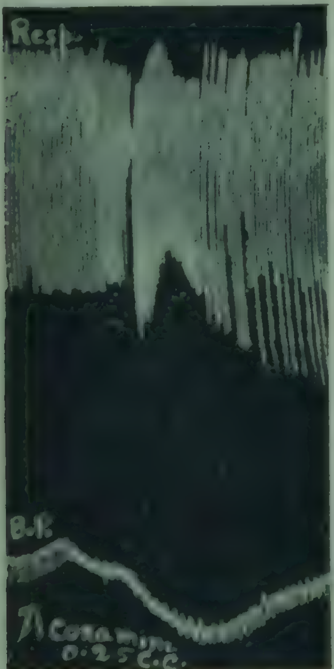


Fig. 6.

Fig. 7.

Fig. 6.—Dog under paraldehyde. Showing effect of coramine (0.25 c. c.) on blood pressure and respiration. Note fall of blood pressure, stimulation of respiration, temporary apnoea followed by increase in rate and depth.

Fig. 7.—Cat under chloralose. Showing effect of coramine on respiration and blood pressure after half an hour of giving morphine to depress the respiration. Note effect on respiration, which is increased both in rate and depth almost immediately ; no effect on blood pressure.

Heart and circulation.—The heart is not influenced in small doses, but there may be some slowing from stimula-

tion of the vagal centre and a small rise of blood pressure from stimulation of the vaso-motor centre in the medulla. The rise of pressure is usually preceded by a fall due perhaps to the stimulation of the inhibitory mechanism. Large doses of nikethamide depress the heart and produce peripheral vaso-dilatation by acting directly on the vessel wall and cause a fall of blood pressure. The action on the heart is indirect caused by stimulation of the respiratory centre thereby improving the oxygen supply to the heart.

The rise of pressure is observed in anaesthetised as also in decerebrate animals but is absent in spinal animals and in animals with denervated carotid sinus. The effect is more marked if a state of depression is present, as happens after administration of some narcotics, *e.g.* barbiturates. It is probable that these drugs increase the sensitiveness of the vaso-motor centre so that a stimulus, which otherwise would be inadequate, will act after the administration of the drugs.

Respiration.—The respiratory centre is stimulated specially if it was depressed ; the rate specially being increased.

Absorption and Elimination.—Leptazol is absorbed fairly rapidly both when given by the mouth or injected subcutaneously. Nikethamide is absorbed more slowly. A small portion of leptazol is eliminated by the kidneys, while nikethamide is largely excreted with the urine. What happens to the rest of the drug in the body is not known.

Fig. 8.—Cat under chloralose. Showing effects of cardiazol on blood pressure and respiration. Note—slight fall of pressure after rise and marked stimulation of respiration.

Therapeutics of Nikethamide and Leptazol

Because of their definite awakening influence in narcotic poisoning, both leptazol and nikethamide are largely used as **analeptics** to revive the patient from a stage of collapse from whatever cause it may arise. Thus they have been used in collapse following volatile anaesthesia, in shock, in secondary cardiac failure, failure of respiration, as for instance, following pneumonia or in overdosage of narcotics, in opium poisoning ; and sometimes with dramatic result in barbiturate poisoning ; and to resuscitate after drowning.

Since they produce convulsion when used in large doses, leptazol has been used in the treatment of schizophrenia, mania, mental depression, melancholia, and other

forms of psychoses. The convulsion is followed by a period of restlessness, confusion and sleep and patients dislike it. Sometimes the treatment is combined with insulin, which is also used in schizophrenia by producing insulin shock. When the two are combined the patient is given the injection when in a state of hypoglycaemic coma, so that he avoids the unpleasantness of convulsion.

Prescribing hints.—Leptazol and nikethamide may be given by the mouth in the form of powder, tablet or solution ; or by subcutaneous injection. Intravenous injection is used for production of convulsion or when rapid action is essential as in the treatment of barbiturate and opium poisoning. For production of convulsion in the treatment of schizophrenia, leptazol is preferred to nikethamide. It should be noted that nikethamide causes respiratory stimulation and rise of blood pressure in doses which produce convulsion. Further, the drug when given intravenously should be introduced very slowly and well diluted to avoid a temporary fall in blood pressure.

PICROTOXINUM

(Picrotox.). $C_{30}H_{34}O_{13}$

Syn.—Cocculin.

Source.—Picrotoxin is a glycoside obtained from the seed of *Anamirta paniculata.*

Characters.—Flexible, shining, prismatic crystals or a microcrystalline powder ; odourless. Stable in air but affected by light. *Soluble* in 334 parts of water ; in 35 parts of boiling water. Readily soluble in dilute acids and alkalies.
B. P. Dose.—1/100 to 1/20 gr. or 0.6 to 3 mg.

Official Preparation

1. **Injectio Picrotoxini.—B. P. Dose.**—By intravenous or intramuscular injection : **1/100 to 1/20 gr. or 0.6 to 3 mg.** N. B. When no strength is given 1/20 gr. in 15 ms. should be dispensed.

Action and Uses

Picrotoxin is a powerful poison producing clonic convulsion from its action on the cerebrum and mid-brain. It stimulates the central nervous system, specially the medulla and cerebral cortex causing acceleration of respiration, rise of blood pressure and slowing of the pulse by stimulating the respective centres. For its stimulant effect on the respiration it has been used in collapse and narcotic poisoning. It checks excessive perspiration possibly by improving respiration and oxygenation of the blood. Picrotoxin antagonises the effects of barbiturate poisoning when as much as 5 to 10 mg. ($\frac{1}{12}$ to $\frac{1}{6}$ gr.), given parenterally, is tolerated and this dose may be repeated if necessary. For the convulsive treatment of mental cases it has been used in the same manner as leptazol and insulin.

Class C : Drugs acting on the Spinal Cord

The cord performs three specific functions, *viz.*—(1) the conduction (*a*) of sensory or afferent, and (*b*) of motor or efferent impressions ; (2) the reflex action ; and (3) the origination of impulses by special nerve centres, e.g.

the sweat centres, located in the cord. The drugs acting on the cord may be divided into *spinal stimulants*, or those which increase the irritability of the anterior cornua and produce convulsions ; and *spinal depressants*, or which depress or paralyse the activity of the anterior cornua and stop convulsions.

1. Convulsants

Drugs which stimulate the general nervous system cause exaggerated reflexes, and if the stimulation is sufficiently strong may produce convulsions, which may be *clonic* or *tonic*. Many factors contribute to the production of convulsions. Thus convulsions are observed in certain diseases due to the presence of toxins in the blood, e.g. in eclampsia, uraemia, high temperature ; in irritation of the brain, as in meningitis, haemorrhage, intracranial growth, embolism ; in children due to reflex effect from some peripheral irritation, e.g. teething, constipation, worms ; in neurotic conditions, hysteria, strong emotion, fright, etc.

Direct stimulation of the cerebrum is as a rule followed by convulsions of a different nature as they are not produced by any sensory stimuli and have not a reflex character in the ordinary sense. They are irregular and only a limited group of muscles are involved and unlike strychnine no inhibition of the antagonist group of muscles takes place. The convulsions correspond to the normal co-ordinated combination of movements, *i.e.* they are *clonic* or epileptiform. Atropine, cocaine, santonin, produce this type of convulsion. Medullary stimulation, as from camphor, leptazol, nikethamide and picrotoxin, also produce clonic convulsions, but these are more irregular and asymmetrical.

Convulsions induced by strychnine are spinal and reflex in character. They are *tetanic*, and other drugs which act like strychnine, but in a milder way, are caffeine, ammonia, cocaine and thebaine.

NUX VOMICA

Nux Vomica. (Nux Vom.)

Syn.—Poison-nut, *Kuchila*, Beng., Hind.

Source.—The dried ripe seeds of *Strychnos Nux-vomica*. Contains not less than 1.2 p.c. of strychnine.

Characters.—Disc-shaped, nearly flat, sometimes irregularly bent, 10 to 30 mm. in diameter, about 4 to 6 mm. thick ; rounded or somewhat acute at the margin. Surface ash-grey, covered with short satiny hairs. Taste, intensely bitter. No odour.

Composition.—(1) *Strychnine*, 0.2 to 0.5 p.c. varying in different seeds, (2) *Brucine*, 0.5 to 1 p.c. (3) *Caffeo-tannic acid* with which strychnine and brucine are united. (4) *Loganin*, a glycoside.

Nucis Vomicae Pulvis.—Powdered Nux Vomica.—Yellowish grey.

Nux Vomica Praeparata. Syn.—Nux Vomica Pulverata.—Prepared Nux Vomica is Nux Vomica reduced to a fine powder and adjusted, if necessary, either by admixture of powdered exhausted nux vomica, or powdered lactose, to contain 1.2 p. c. strychnine; or 4 grs. contain 1/20 gr. of strychnine.

B. P. Dose.—1 to 4 grs. or 60 to 250 mg.

Official Preparations

1. **Extractum Nucis Vomicae Siccum.**—Contains 5 p.c. of strychnine; or 1/20 gr. in 1 gr. **B. P. Dose.—1/4 to 1 gr. or 15 to 60 mg.**
2. **Extractum Nucis Vomicae Liquidum.**—Contains 1.5 p. c. w/v of strychnine; or 1/24 gr. in 3 ms. **B. P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.**
3. **Tinctura Nucis Vomicae.**—Contains 0.125 w/v of strychnine; or 1/30 gr. in 30 ms. **B. P. Dose.—10 to 30 ms. or 0.6 to 2 mils.**

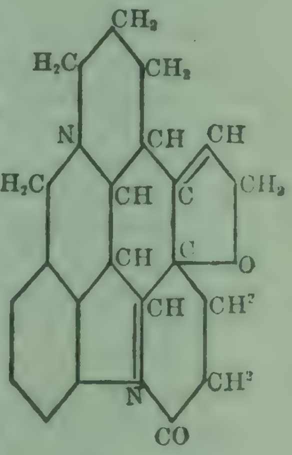
STRYCHNINAE HYDROCHLORIDUM. (Strych. Hydrochlor.). Strychnine Hydrochloride is the hydrochloride of the alkaloid strychnine. Colourless, prismatic crystals. Very bitter. *Solubility.*—1 in 40 of water, 1 in 80 of alcohol (90 p.c.).

B. P. Dose.—1/30 to 1/8 gr. or 2 to 8 mg. By subcutaneous injection: 1/30 to 1/16 gr. or 2 to 4 mg.

Official Preparations

1. **Liquor Strychninae Hydrochloridi.—Contains 0.82 p. c. w/v of strychnine or 1/8 gr. in 12 ms. B. P. Dose.—3 to 12 ms. or 0.2 to 0.8 mil.**
2. **Injectio Strychninae Hydrochloridi.—B. P. Dose.—Subcutaneously, 1/30 to 1/16 gr. or 2 to 4 mg. N. B. If no strength is stated a solution containing 1/16 gr. in 15 ms. shall be dispensed.**

Pharmacology



Strychnine

Internally. **Gastro-intestinal tract.**—Being intensely bitter both nux vomica and strychnine are typical **stomachics** and **tonics,** increasing the secretion of gastric juice, and thereby sharpening appetite and promoting digestion like gentian, calumba, etc., but more powerfully. They increase the tone and peristaltic movements of the intestines by augmenting the reflex excitability of the Auerbach's plexus and may thus act as a purgative in chronic constipation due to colonic atony. For the same reason it tones up the bladder and is useful in all conditions of atony of the plain muscles. The preparations of the crude drug (dry extract or the tincture), being less easily absorbed, remain for a longer time in the intestine and act better than the alkaloid.

Heart and circulation.—The heart is not affected in therapeutic doses of strychnine, but there may be some slowing of the pulse from stimulation of the vagus centre and a rise of blood pressure from **stimulation of the vasoconstrictor centres in the medulla and cord.** The vessels of the splanchnic area are constricted, while those of the heart, lungs, skin (atropine effect) and central nervous

system dilate. The general effect therefore is to raise the arterial pressure and allow more blood to flow through those organs necessary for the maintenance of the vital processes. This redistribution of the blood recuperates the heart by improving coronary circulation, thereby supplying more oxygen and nutrition. This effect is only observed in full therapeutic doses. It stimulates the secretion of adrenaline and thus may indirectly produce circulatory effects.

Respiration.—The medullary and spinal respiratory centres are stimulated rendering the respiration deeper and quicker. The effect is more marked when the centre is depressed by some narcotics. In toxic doses the respiratory muscles participate in the general tetanus and the patient dies asphyxiated from rigidity of the thoracic muscles and diaphragm.

In therapeutic doses the bronchial muscles are improved in tone, and although this may make it useful in relaxed conditions of the bronchus it will be harmful in spasmodic state of the bronchi, as in asthma. The cough centre is also stimulated.

Brain.—The higher centres are stimulated though feebly even in toxic doses and the mind remains clear to the last, and the patient feels the excruciating pain of convulsion. Small doses render the special senses more acute. Thus it strengthens the mental power and sharpens the senses of sight, smell and hearing and pain is more keenly felt. It increases the field of vision and makes the eye more sensitive to slight differences in light, due to its effects on the retinal cells and not to changes in the brain.

Medulla and Cord.—Strychnine **stimulates** the **respiratory,** the **vaso-motor,** and to a less extent the cardiac vagal centre. All these become very excitable. But its main action is on the cord. In moderate doses it increases the tone of the muscles, *i.e.* produces exaggerated reflexes, and makes the cord hypersensitive, so that a slight stimulus, which ordinarily causes no marked response, is followed by increased reflex excitability. In poisoning, a slight peripheral stimulus, like the prick of a pin or a flash of light or a sound, will provoke **convulsions** which are sudden in onset and involve all the voluntary muscles of the body. They are at the beginning intermittent, but subsequently become **tetanic,** and although appear to be spontaneous are in reality always elicited by some external stimulus. That the convulsions are not cerebral is shown by the fact that they can be produced in a decapitated animal. Moreover, if the posterior nerve roots are divided, or if the entire surface of the skin is anaesthetised by cocaine so that no afferent impulse can reach the spinal cord, no convulsion follows. If however, the central ends of the cut

erves are stimulated, convulsions can be obtained. The convulsions therefore have their origin in the cord, though not initiated there ; they are reflex, being the result of afferent impulses to external stimuli.

Ordinarily when a stimulus is applied, as elicited by an ordinary simple reflex, it will not only cause contraction of one group of muscles, but by co-ordination will cause relaxation of the corresponding antagonists group of muscles (Sherrington). Thus there are two components working, one the motor and the other inhibitor. The stimulation of the flexor muscles will lead to inhibition of its antagonist, the extensor muscles and both cannot be put into action simultaneously unless the stimulus is abnormally strong. After a toxic dose of strychnine the contraction is not limited to the usual group but also involves the opposing group of muscles, *i.e.* the flexors and extensors contract simultaneously. Strychnine therefore causes a breakdown of the normal inhibitory influence and produces contraction of all the groups of muscles, and of the two sets of opposing muscles, the effect of the strongest set predominates. Therefore in case of poisoning the body becomes arched backwards (opisthotonos), the angles of the mouth are drawn back (risus sardonicus), and owing to the involvement of the diaphragm and the muscles of the chest and abdomen, the respiration becomes affected.

Nerves and muscles.—Strychnine augments the capacity for muscular work and delays onset of fatigue. It has no effect on the voluntary muscles although their tone is improved through the cord. In toxic doses the terminations of the motor nerves are paralysed. This is not due to the exhaustion of the nerve tissue as has been supposed, but to the direct action of the drug on the nerves themselves.

Metabolism.—The increased movements of the body naturally excite oxidation, and the absorption of oxygen and excretion of carbonic acid are correspondingly increased. Owing to increased flow of blood through the skin there is a rise in the skin temperature but there is more heat dissipation, and any rise of temperature from increased metabolism is counteracted, and the net result is rather a fall of temperature. Glycogen in the liver and of the muscles is considerably reduced during the spasm and may disappear entirely if the spasms be of some duration. Sugar is also passed in the urine of animals exprimented on. This is probably a secondary effect due to the liberation of adrenaline.

Absorption and clearance.—Strychnine is rapidly absorbed mainly from the intestine most of which is taken up by the liver where it undergoes oxidation. The rest is excreted chiefly in the urine (10 to 20 p. c.). The excre-

tion begins within a few hours and continues usually f forty-eight to seventy-two hours, though traces may b found even after five days. Clearance is therefore slow

Toleration.—Some persons are more tolerant tha others. Some people of India are in the habit of takir nux vomica morning and evening with *pan* ; commencir with $\frac{1}{4}$ gr. they sometimes increase it to about 20 grs. (a entire nut). In some instances toleration is not induce rather the nervous system becomes hypersensitive.

Acute toxic action.—Within half to one hour after a large a poisonous dose, the symptoms of poisoning commence. General u easiness and soreness of the limbs, instantly followed by shootir pains in the back and then down the arms and legs, are first observe Tetanic convulsions of the muscles soon set in, lasting for half one minute, when they relax, leaving the patient sweating and e hausted. They come on again and again and the intermission ge shorter and shorter as the severity of the symptoms increases. Th muscles of the jaw are only affected before death, not in the begi ning. In short, the symptoms of poisoning closely resemble tho of tetanus, from which they differ in (1) their rapid development (2) want of a history of a wound, operation, etc., as in tetanus ; (3 complete relaxation between the spasms in strychnine poisonin whereas in tetanus the muscles of the back and jaw remain rig between the spasms ; (4) trismus or "lock-jaw" only appears as late symptom, whereas it is the first symptom in tetanus ; (5) deat taking place soon, or the symptoms rapidly declining.

Treatment.—Pump before convulsions, or under chloroform aft convlusions. Apomorphine 1/10 to 1/2 gr. subcutaneously, emetics ; tannin or any preparation containing it to form insolub tannate, which should be quickly removed before it is broken u again in the stomach. Activated charcoal adsorbs the poison, fo lowed by potassium permanganate to destroy the same. For co vulsions, use luminal sodium, amytal or nembutal, or magnesiu sulphate, any of which may be given intravenously ; large dose bromides for prolonged effect, chloroform inhalation, artificial re piration, and oxygen, etc.

Fatal dose.—3 grs. by mouth, but only 1/2 gr. if absorbed.

THERAPEUTICS

Internally. **Gastro-intestinal tract.**—Nux vomica ar strychnine are largely used to promote appetite and dige tion in **atonic dyspepsia** and **weakness of digestion** durir convalescence from acute illness. Tincture of nux vomic and infusion of calumba or infusion of gentian make a ve efficient prescription for such cases.* Strychnine ha given satisfactory results in acute and chronic gastr **catarrh** and **gastralgia** ($\frac{1}{100}$ gr. hypodermically). Becau it increases peristalsis, nux vomica is frequently given an adjunct to purgatives.

Heart and circulation.—Its beneficial effect in cardi failure is doubted by many, but it has been found use at the Mayo Clinic as a supplementary medication in au

*Sod. bicarb.	grs. 15	*Acid. hydrochlor. dil.	ms. 10
Sp. ammon. aromat.	ms. 15	Tinct. nuc. vom.	ms. 10
Tinct. nuc. vom.	ms. 10	Sp. chlorof.	ms. 15
Inf. calumb. rec.	ad. oz. 1	Inf. gentian. co.	ad. oz. 1

-ular **fibrillation** if quinidine alone does not restore normal rhythm. It is supposed to augment the action of quinidine when used in doses of $\frac{1}{60}$ gr. (1 mg.) three times daily. The chief use of strychnine is in cases of pure failure of circulation due to vascular paralysis leading to collapse, such as may occur during the crisis of pneumonia. Its action is indirect through the stimulation of the respiratory and vasomotor centres.

Respiration.—As it stimulates the cough centre, it helps expectoration by provoking coughing, and is useful in chronic bronchitis, protracted pneumonia, etc., when given with other expectorants. As a respiratory stimulant it is valuable during anaesthesia, surgical shock, poisoning by barbiturates and other narcotics, etc., and in exhaustion of the centre, as in **pneumonia.** In these conditions improved respiration will result in increased supply of oxygen to the heart and the central nervous system, and there will be a break in the vicious circle thus enabling the patient to maintain the effect even after the stoppage of the drug. To be of any value it should be given in doses of $\frac{1}{30}$ to $\frac{1}{18}$ gr. and repeated every 4 to 6 hours.

Nervous system.—As a spinal stimulant strychnine is used in diseases of the nervous system, but the conditions in which it can be of service are very limited, and its use requires careful judgment. It is useful in (*a*) *paresis* or incomplete paralysis ; (*b*) *local paralysis* as that of the forearm, larynx, sphincter, etc., due to any toxic agent, as lead, alcohol, or tobacco ; (*c*) *diphtheritic paralysis* ; and (*d*) *post-operative paralysis* of the stomach or intestine. It should not be used (*a*) when the paralysis is of recent origin ; (*b*) when rigidity of muscles still exists ; (*c*) when there is much wasting of muscles ; (*d*) when lead symptoms are present ; and (*e*) when the muscles do not respond to electricity.

Besides the above, nux vomica or strychnine can be used in atonic conditions of the bladder and sexual debility. In mental depressions from over-work it should be used after the suspension of work.

2. Anticonvulsants

The different factors which produce convulsion have already been discussed. (*See* page 222). Drugs which depress the cerebrum or the spinal cord are selected for the treatment of convulsion. They are bromides, chloral hydrate, phenobarbitone, and in urgent cases general anaesthetics or magnesium sulphate injection.

Selection of a suitable anticonvulsant drug for the treatment of epilepsy, where it has to be used for a prolonged period, without producing any permanent damage to the brain or other vital organs, has not been very easy

For years, bromides were considered as the only drug i this disease. It was soon realised that to keep the patien free from fits the drug had to be continued for months o years, which often left in its trail undesirable effects o more or less permanent nature. Phenobarbitone, though an improvement over bromides, also depresses not onl the motor cortex but the sensory area of the brain as well Attempts have been made to obtain a drug which wil depress the motor area only and thus control epilepti seizures and at the same time will be free from any toxi effects.

The next advance in this direction was the introduc tion of some compounds related to the barbiturates, namely phenytoin sodium (dilatin sodium), methylphenobarbiton (prominal), and methoin (mesontoin). These depress only the motor cortex and not the sensory area to any appre ciable extent. In troxidone (tridione) we have a remedy useful in petit mal, psychomotor, akinetic and myocloni forms of epilepsy. Mephenesin (myanesin) also depresse the central nervous system and diminishes reflex excit ability of the spinal cord and acts as a muscular relaxan and anticonvulsant. All these drugs raise the convulsiv threshold and antagonise the effect of convulsant drug like strychnine, picrotoxin, leptazol, etc.

TROXIDONE. (Not official). **Syn.**—Tridione ; Trimethadione— It is 3, 5, 5-trimethyloxazolidine-2, 4-dione. It is an **analgesic** an mildly **sedative** and has been recommended for the treatment o **epilepsy,** specially petit mal, myoclonic jerks and akinetic (loss o posture) seizures in epilepsy. It is specially valuable in attack which are sudden, brief and stereotyped, usually occurring in childre and are of frequent occurrence, often several times a day. Ele troencephalogram (E.E.G.), usually, though not always, shows th wave-and-spike form of abnormality. It may aggravate the liabili to other types of attack.

It is not without danger, cases of nephrosis, nausea, vomitin photophobia and skin rashes have been recorded ; also, though rarel aplastic anaemia and agranulocytosis.

The **dose** is regulated according to the response of the patien 1 to 2 grm. in divided doses daily of 0.3 grm. (5 gr.) each. *F infants* 0.3 grm. (5 gr.) daily ; children (2 to 4 years), 0.6 gr (10 gr.) and over 5 years, 0.9 grm. (15 gr.) daily.

Methoin. (Not official). **Syn.**—Methylphenylethyl Hydantoi Mesontoin.—It is another hydantoin derivative having action simil to phenytoin sodium (dilantin) but less toxic. When for prolong use chances of toxic effects are apprehended with phenytoin, metho should be used. For an adult 0.1 grm. (1½ gr.) should be given da at the beginning for one week in addition to the usual dose of sodiu phenytoin. This latter drug should be reduced by 0.1 grm. a replaced by methoin. and week by week a further exchange sho be made until sodium phenytoin has been entirely replaced methoin, and the dose of this drug should be increased weekly t the desired effect is obtained. Generally 0.3 or even 0.6 grm. (5 10 gr.) are required for grand mal seizure.

Toxic action.—Sometimes nausea, headaches, listlessness, dro siness, nervousness and fullness in the head are complained of, wh

used for a prolonged period. A common side effect is cutaneous rash which may be serious in patients with skin sensitivity.

Mephenesin. (Not official). **Syn.**—Myanesin.—It is α : ß-dihydroxy- -(2-methylphenoxy) propane. A synthetic compound with depressant action on the central nervous system. It is used as a muscular relaxant like tubocurarine in general anaesthesia. It differs from curarine in that its site of action is on the spinal cord and not the neuromuscular junction. Because it diminishes the reflex excitability of the spinal cord, it is of special value in the treatment of strychnine poisoning. It is also used in hyperkinetic states and Parkinsonism, and is an effective anticonvulsant in status. Besides being a muscular relaxant and anticonvulsant, it also possesses some analgesic action and has been used in psychiatric practice with some success. The only side-effects are venous thrombosis at the site of injection and haemolysis.

Dose.—15 to 45 grs. or 1 to 3 grms. *Intravenously* :—10 to 15 mg. kg. (10 p.c. solution in organic solvents is liable to produce thrombosis and haemolysis ; 2 p.c. solution in normal saline is however better) as a muscle relaxant in general anaesthesia.

CLASS D : Drugs acting on the Autonomic Nervous System

The voluntary muscles are under the direct control of the central nervous system, but the activity of the involuntary muscles and of the glands is regulated by a more complex arrangement. A characteristic feature of these involuntary active organs is that they can work independently of the central nervous system and for this reason their nervous system is known as *autonomic system.* The autonomic nervous system has been classified into (1) *cranial autonomic* ; (2) *sympathetic proper* ; and (3) *sacral autonomic.* The cranial and sacral autonomic systems have complementary physiological functions and are known as *parasympathetic system.*

It must however be clearly understood that this system is part of the general nervous system with which it works in close harmony. Fulton has shown that the sympathetic and parasympathetic systems are regulated by centres in the hypothalamus, which also regulates emotion and metabolism. Thus psychical stimulation, e.g. fright, excitement or emotion, is followed by changes in the activity of the heart (acceleration), vessels (flushing), even of different secretions (sweat).

Apart from the central control, the activity of the sympathetic and parasympathetic is related to the internal secretions of the different ductless glands. Thus stimulation of the adrenergic nerves is followed by an increased secretion of adrenaline which activates all organs supplied by this nerve. Thyroid secretion causes increased tone and sensitises the tissues to the action of adrenaline, whilst deficiency of thyroid secretion is followed by increased vagal tone.

The *sympathetic system proper* consists of a chain o ganglia or collections of nerve cells situated on each sid of the vertebral column. The "outflows" from the sym pathetic arise from the dorsal and down to the fourth an fifth lumbar nerves as minute medullated fibres. Thes have their cell stations in the ganglia of the sympatheti cord, and in the cardiac, solar and hypogastric plexuses.

The "outflows" from the *parasympathetic* include th cranio-bulbar and the sacral outflows. The cranial grou is formed by the third, the seventh, the ninth and th tenth ; while the sacral group by the second, the third an the fourth sacral nerves. The parasympathetic fibre which run into the oculo-motor arise from the mid-brai and supply the ciliary muscle and the iris. The sevent and the ninth emerge from mid-brain and supply the vaso dilators and the secreting glands in the nose, the mout and the pharynx. The chorda tympani becomes bound u with the branches of the fifth and is distributed with them Finally, from the mid-brain emerge the vagi which suppl the heart, the bronchial muscles, the oesophagus, th stomach and the small intestine, and also regulate th secretory mechanism. The fibres from the sacral regio supply the vaso-dilators, the external generative organs the bladder, the rectum, the anus, and motor fibres to th musculature of the descending colon and rectum. It wi be seen that the autonomic fibres arise only from certai sections and not in an unbroken succession from the centra organs, and act as conducting paths to carry impulses fro the central nervous system to the different internal organs and by means of their endings either augment or depres their functions. All the functions of these organs are per formed even if the organs concerned are separated fro the control of the central nervous system.

The sympathetic and the parasympathetic system are antagonistic to each other both physiologically an frequently pharmacologically. In most organs where th two types of nerve influences act, they affect their func tions in opposite directions, *i.e.* they lead to opposite re sults. Thus the pupil is contracted by the parasympathe tic fibres running along the third nerve, while it is dilate by the sympathetic supplying the dilator pupillae. Sim larly, the parasympathetic vagus inhibits the heart, whil the sympathetic accelerates it. It must not be suppose that the sympathetic alone is concerned with augment tion and the parasympathetic with inhibition. Thoug the vagus is the inhibitor nerve of the heart, it is the mot to the bronchial muscle. Similarly, the sympathetic is i hibitory to the intestine and the coronary arteries. Son organs are innervated by one division only, e.g. the uter and most arterioles are supplied by the sympathetic onl

while the glands of the stomach and pancreas by parasympathetic only.

Dixon pointed out that after stimulation of the vagus nerve to the heart a substance could be extracted from the heart muscle which was inhibitory in its action on other hearts, and which effect could be antagonised by atropine, just as it antagonises vagus stimulation. This work was subsequently revived by Dale and Loewi, who have shown that these drugs act not by stimulating the nerve-endings but by liberation of certain chemical substances, *viz.* acetylcholine, or adrenaline-like substance termed *sympathin*. The sympathetic post-ganglionic fibres liberate at their ends substances identical with adrenaline, and similarly the parasympathetic post-ganglionic fibres liberate acetylcholine at their terminals; whereas all the pre-ganglionic fibres (whether they belong to the sympathetic or the parasympathetic system) liberate acetylcholine at their ganglia (excitor neurones), and this substance probably stimulates the excitor cells to discharge a fresh group of nervous impulses. Drugs which stimulate the sympathetic act not because of the physical stimulation but by the formation of sympathetic hormone, adrenaline, around the cell. Similarly, those stimulating the parasympathetic act by the formation of the hormone, acetylcholine. Dale suggested that the nerve fibres which liberate, at their terminals, bodies resembling adrenaline or acetylcholine, should be called "adrenergic" or "cholinergic." Adrenergic fibres are therefore only present in the post-ganglionic fibres of the sympathetic, but the cholinergic fibres include the post-ganglionic fibres of the parasympathetic system and all the pre-ganglionic fibres of both the sympathetic and parasympathetic systems. The motor nerves to the skeletal muscle and the antidromic vaso-dilators in the posterior nerve roots also act in the same way.

Certain post-ganglionic fibres anatomically belonging to the sympathetic system (sympathetic supply to the sweat glands) act like parasympathetic by liberating acetylcholine. In other words they are cholinergic and functionally should be regarded as part of the parasympathetic system.

According to this theory atropine and ergotoxine act directly on the cells and render the tissues insensitive to acetylcholine or adrenaline, thus preventing the effects of parasympathetic or sympathetic stimulation as the case may be. Physostigmine and neostigmine produce their main effect by a mechanism depending on substrate competition, *i.e.* they compete with acetylcholine for the enzyme choline esterase with the result that a higher con-

centration of physiologically active acetylcholine is liber-
ated.

Choline esterase is the specific enzyme contained in blood an tissues which splits acetylcholine to choline and acetic acid. Thi choline is pharmacologically weak as compared to acetylcholine possessing only 1/100,000th of the vaso-depressor potency of its pre cursor. The enzyme exists in tissues specially when acetylcholin is liberated by nerve impulses. The action of this enzyme is rapi and of brief duration. When this enzyme is inactivated by physos tigmine and neostigmine the action of acetylcholine is more pro longed.

Sympathin is the chemical mediator of the excitatory proces initiated by sympathetic nerve impulses and bears close resemblanc to adrenaline in its pharmacological properties and perhaps i chemical structure. Whereas adrenaline has both excitatory an inhibitory effects, sympathin on the other hand though possesse these two actions, they are separable. Whereas ergotoxine block the rise of blood pressure produced by adrenaline, it has no suc effect on blood pressure rise by sympathin.

These facts led Cannon and Rosenblueth* to postulate the forma tion in the cells affected by the sympathetic of two forms of sympa thin, namely, sympathin E, which is formed when the action is a excitatory one, and sympathin I, formed when the effect is inhibi tory. Different tissues produce different amount of sympathin I and sympathin I ; thus the liver produces chiefly E, and the gastro intestinal tract both E and I ; the heart produces E from the cardia muscles and I from the coronary vessels. Hence the varyin effects produced on other organs when these substances get into th blood streams. It has been suggested that sympathin E is **nor adrenaline** also known as **artrenol** which is the immediate precurso of adrenaline from which it differs by the absence of a methyl grou on the nitrogen atom.

Drugs acting on the sympathetic system.—The sympatheti fibres have two actions, *augmentor* and *inhibitor*. The augmento effects are acceleration of the heart, vaso-constriction, dilatatio of the pupil, increased secretion of saliva, tears, etc. The inhibitor effects are chiefly confined to the stomach, intestine, gall-bladde bronchi, and the urinary bladder. It has also an inhibitory effec on the virgin uterus of cat.

(*a*) *Drugs which stimulate the sympathetic endings.*—Adre naline, ephedrine, tyramine, and ergotoxine in small doses. Cocain increases the peripheral excitability without directly stimulating i

(*b*) *Drugs depressing the sympathetic endings.*—Ergotoxin in large doses paralyses the motor fibres of sympathetic ; ergotamin and apocodeine.

Drugs acting on the parasympathetic system.—Parasympa thetic stimulation causes slowing of the heart, contraction of th pupil, spasm of the bronchial muscles, increased secretion of a glands centrally innervated, *viz.*, sweat, saliva, stomach and contrac tion of the intestines, and most plain muscles. The urine, secretio of bile, milk and the internal secretions are not affected by thi system.

(*a*) *Drugs stimulating the parasympathetic endings.*—Mus carine, pilocarpine, physostigmine, neostigmine, carbachol an acetylcholine.

(*b*) *Drugs depressing the parasympathetic endings.*—Atro pine, hyoscyamine, hyoscine. They produce results opposite to stim ulation.

The result of sympathetic and parasympathetic stimulation o

* *Cannon and Rosenblueth, Amer. J. Physiol.*, 1933, 104, 557 : 1935, 113, 25

the different organs is set out in the following table. But it should be remembered that the function of certain nerves is still uncertain.

The effects of Sympathetic and Parasympathetic stimulation on different organs.

Organ	Sympathetic	Parasympathetic
Eye	Pupil : Dilatation from stimulation of the radiating fibres.	Pupil : contraction from stimulation of circular fibres.
	Ciliary ms. : relaxation.	Ciliary ms. : contraction.
Bronchioles	Muscles : relaxation.	Muscles : contraction.
	Glands : nil.	Glands : increased secretion.
Alimentary canal	Relaxation, except the sphincters which contract. Secretion : inhibition.	Augmentation of peristalsis except the sphincters which relax. Secretion : increased.
Heart	Acceleration of rate.	Slowing of rate.
Arterioles	Constriction, except coronary vs. which dilate.	Nil as a rule.
Uterus	Mixed effect. Excitation or inhibition depending on the preponderance of particular nerves whether motor or inhibitory.	Nil.
Bladder	Relaxation, except the sphincter which contracts.	Contraction except the sphincter which relaxes.
Salivary glands	Slight viscid secretion.	Increased secretion and vaso-dilatation.
Sweat glands	Though supplied by sympathetic they act as if they are supplied by parasympathetic. Therefore perspiration is induced by parasympathetic stimulants and inhibited by parasympathetic depressants, *i.e.* the fibres are cholinergic.	

1. Drugs Acting on the Eye

Drugs acting on the pupil.—The iris is the regulator of the pupil. It is composed of two sets of fibres, the circular which contract, and the radiating which dilate. These sets of muscles are in constant action, and by opposing each other constitute a sensitive balanced mechanism for the regulation of the size of the pupil. The sphincter iridis (circular fibres) is supplied by the third or oculomotor, which arises from the mid-brain, and the centre for the contraction of the pupil is located in the corpora quadrigemina. Stimulation of the third nerve contracts, and its section dilates the pupil. The cervical sympathetic is the nerve for the radiating fibres ; its stimulation causes dilatation and its division, contraction of the pupil. The oculo-motor centre is kept under control by impulses passing from higher centres, and if these higher centres are inhibited, as during sleep, during surgical anaesthesia and in opium poisoning there is contraction of the pupil (Meyer and Gottlieb).

Mydriatics or pupil dilators act as follows :—

1. *By paralysing the oculo-motor nerve-endings*, as atropine, hyoscine, homatropine.

2. *By stimulating the endings of the cervical sympathetic*, as cocaine, adrenaline, ephedrine and tyramine.

3. *By depressing the oculo-motor centre*, as in asphyxia, general anaesthetics (fourth stage).

Strong emotion, fear, excitement and asphyxia dilate the pupil either by stimulating some centres of the sympathetic nerve supplying the eye and simultaneous inhibition of the oculo-motor centre, or by stimulating the sympathetic supply of the adrenal gland and causing an increased secretion of adrenaline.

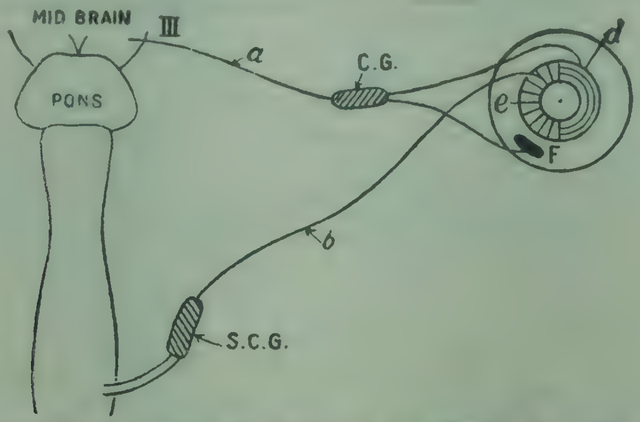


Fig. 9.—Explaining Action of Drugs on the Pupil. III.—3rd nerve showing the pre-ganglionic parts and the endings supplying the circular fibres of the iris (d) and the ciliary muscles (F). S. C. G., superior cervical ganglion and sympathetic (b) supplying the radiating fibres of the iris (e).

Myotics or pupil contractors act as follows:—

1. *By stimulating the endings of the third nerve*, as acetylcholine, carbachol, pilocarpine, physostigmine, muscarine.

2. *By stimulating the centre for contraction*, as opium, picrotoxin, general anaesthetics in the early stage.

Nicotine, coniine and lobeline first stimulate and then depress the ganglion cells, therefore the pupils first contract then dilate.

Drugs that impair accommodation.—Ciliary muscle adjusts the lens for distant and near objects of vision. During rest, the lens remains flattened, but to see near objects it becomes more convex owing to the drawing in of the ciliary processes by the contraction of the circular fibres. It is supplied by the third nerve. Drugs that paralyse accommodation by acting on the ciliary muscle are called *cycloplegic* ; as atropine.

Drugs affecting the intra-ocular tension.—The normal tension depends upon (*a*) the amount of intra-ocular secretion, (*b*) the freedom with which fluids may escape through the lymph channels (spaces of Fontana) into the canal of Schlemm. Tension may be raised by extra secretion or by dilatation of the pupil which shuts off the spaces of Fontana.

1. *Drugs increasing the intra-ocular tension*, atropine, hyoscine and hyoscyamine.

2. *Drugs decreasing the intra-ocular tension*, pilocarpine and physostigmine.

2. Drugs Stimulating the Parasympathetic endings.
(Parasympathomimetic Drugs)

Muscarine, an alkaloid derived from poisonous mushroom, *Amanita muscaria*, has the same pharmacological action as pilocarpine except that it produces more nausea and vomiting. It is not used therapeutically.

CHOLINE
(Not Official)

A syrupy liquid occurs in organ extracts, many vegetables, ergot, and as a decomposition product of lecithin. It has been isolated from washed portions of intestine of rabbit, dog and cat.

Acetylcholine.—The acetyl derivative of choline. Prescribed in the form of **Acetylcholine Hydrochloride.** A white hygroscopic powder. *Dose.*—3/4 gr. or 50 mg. subcutaneously or intramuscularly. Dangerous intravenously and ineffective when given orally.

CARBACHOLUM

(Carbachol.)

Syn.—Doryl : Choryl : **Moryl.**

Source.—Carbachol is carbamylcholine chloride and may be obtained by the interaction of **β-chloroethyl** carbamate and trimethylamine. It contains not less than 99.5 per cent. of $C_6H_{15}O_2N_2Cl$, calculated with reference to the substance dried at 100°C.

Characters.—Small, colourless, hard prismatic crystals, or a crystalline powder ; odour, faint, resembling that of an aliphatic amine ; markedly hygroscopic in moist air, very soluble in water ; very slightly soluble in dehydrated alcohol at 20°C, but dissolves more readily on boiling and separates on cooling, in transparent, highly refractive prisms. Almost insoluble in acetone and in solvent ether.

B. P. Dose.—1/60 to 1/16 gr. or **1 to 4 mg.** By subcutaneous injection.—**1/240 to 1/120 gr.** or **0.25 to 0.5 mg.**

Official Preparation

1. **Injectio Carbacholi.—B. P. Dose.—1/240 to 1/120 gr.** or **0.25 to 0.5 mg.** N.B. When no strength is stated, solution containing 1/240 gr. in 15 ms. should be dispensed.

Pharmacology and Therapeutics

It has been pointed out that acetylcholine is liberated at the nerve-endings and is responsible for the effects on the tissues when cholinergic nerves are stimulated. The action of acetylcholine is short lived as it is destroyed by specific enzyme choline esterase. This destruction is prevented by physostigmine and neostigmine which inhibit the action of esterase, and a preliminary use of any of these prolongs the action of acetylcholine.

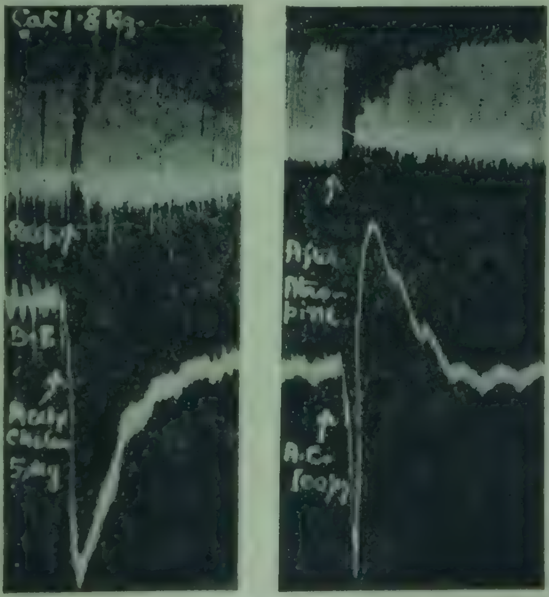


Fig. 12.—Cat under chloralose. Showing effect of acetylcholine on blood pressure (left) and after atropine (right). Note the fall in pressure. After atropine, which blocks the parasympathetic effects, acetylcholine causes a rise of pressure showing that acetylcholine stimulates the sympathetic ganglia.

Acetylcholine is about 10,000 to 100,000 times more

powerful than choline, and possesses the following actions, viz., (1) it *dilates the vessels* and causes a fall of blood pressure, this effect is direct ; (2) *stimulates the post-ganglionic fibres of the parasympathetic* like muscarine, *i.e.* causes greater fall of blood pressure, increased secretion of salivary, lachrymal, intestinal and also the sweat glands which are innervated by the sympathetic but contains cholinergic fibres ; (3) *first stimulates and then paralyses the autonomic ganglia* (nicotine effect). This can be elicited by giving acetylcholine after atropine which paralyses the parasympathetic vagus ; and (4) *stimulates the ends of all motor nerves to skeletal muscles.*

It increases the movements of the oesophagus, stomach, intestine and bladder.

In large doses the fall of pressure is great due largely to vagus effect on the heart (slowing of rate and weakening of contraction). As a rule the muscarine action is more marked than the nicotine effect. Thus an intravenous injection causes fall of blood pressure. The nicotine effect is characterised by first stimulation and then paralysis of the autonomic ganglia of both the sympathetic and parasympathetic nerves. The result will therefore vary with the dose. Since atropine paralyses the parasympathetic endings, use of acetylcholine after atropine will produce a rise of blood pressure by stimulating the sympathetic ganglia. If nicotine is used in large doses which paralyse the ganglia this pressor effect is not observed.

In man acetylcholine produces little effect except vasodilatation and slight fall of blood pressure due to its rapid destruction and to the efficient compensatory cardio-vascular reflexes mediated through vasosensitive carotico-aortic receptors. This is supplemented by sympatho-adrenal discharge through nicotine effect which counteracts any alterations in the heart and blood vessels. Very little effect is observed in the stomach and intestine even in large doses except nausea and vomiting.

Carbachol has the same action as acetylcholine but is a more stable compound as it is not inactivated by the enzyme choline esterase. Its action is therefore more prolonged and since it is not decomposed in the stomach it can be administered orally. As compared to acetylcholine, its action is greater on the gastro-intestinal canal and bladder and less on the cardio-vascular system. It is therefore largely used in **post-operative intestinal atony**, and post-operative **retention of the urine.** It may also be used for similar conditions associated with organic nervous disorders which render complete emptying of the bladder ineffective. When a rapid action is desired it may be given subcutaneously or intramuscularly in doses of $\frac{1}{240}$ gr. and repeated if necessary after half an hour.

For its vaso-dilator effect it is used in Raynaud's disease, intermittent claudication, essential hypertension, and paroxysmal tachycardia. It has also been used in myasthenia gravis.

Because of its myotic action and because it lowers intra-ocular tension, carbachol is used for application to the eye in 0.75 p. c. solution in glaucoma.

Contra-indications.—It is contra-indicated in acute failure of the heart or peptic ulcer. Some patients complain of sweating, nausea and faintness, but these are seldom serious and can be obviated by atropine.

Choline forms part of vitamin B-complex. Lecithin contains choline and casein contains both choline and methionine. It has been shown that administration of choline to depancreatised dog lowers the deposition of abnormal liver fat and prevents damage to the liver following administration of carbon tetrachloride and protects the liver of a protein-deficient animal. Both methionine (q.v.) and choline possess this "lipotropic" property. Choline has been used either alone or with methionine in **toxic hepatitis, fatty and cirrhosis** of the **liver.**

It is administered in the form of chloride orally or intravenously, the total dose being 1 to 2 grm. or more daily. It is neutral to litmus and for oral use can be given in capsules. Intravenous use may cause increased secretions, bronchial spasm, intestinal cramps, flushing and perspiration which may require administration of atropine.

Leubret and Pery* recommended injection of *Choline Hydrochloride*, 20 mg. (1/3 gr.) in 1 mil in all stages of tuberculosis and reported favourable result. The treatment is followed by a lowering of temperature, a return of the appetite with a re-establishment of the digestive functions and a gain in weight. When combined with calcium it gives better result in tuberculosis. The usual formula is calcium gluconate 10 p.c. and choline hydrochloride 1/30 gr. in 10 mils of physiological solution.

Non-official Choline Esters

Methacholine Chloride. Syn.—Mecholyl ; Amecol.—Acetyl-ß-methylcholine hydrochloride has action similar to carbachol, and is useful when administered by the mouth or as injection. It has been used under the same conditions where carbachol is indicated. It is para-sympathetic stimulant like acetylcholine but more stable.

Dose.—For oral administration, 3 to 7½ grs. or 0.2 to 0.5 grm.; for subcutaneous injection, up to 25 mg. (2/5 gr.). *It should not be given intravenously.*

Meprochol. Syn.—Esmodil.—It is Trimethyl-methoxy-propenyl-ammonium bromide. A parasympathetic stimulant with special selective action on vagus and pelvic nerves. Used in post-operative paresis of intestine and bladder.

Dose.—1 mil of 0.3 p.c. solution by *subcutaneous* or *intramuscular injection.*

Sympatholytic Drugs

These block the impulse of sympathetic nerves. They are : Ergotoxine, Ergotamine and Tolazoline (Priscol).

* *British Medical Journal, Epitome*, May, 10, 1930.

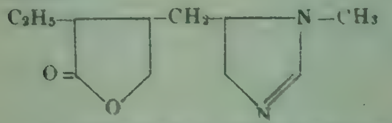
Tolazoline. Syn.—Priscol.—It is 2-Benzyliminazoline. A sympatholytic drug producing peripheral vaso-dilatation. Used in the treatment of peripheral vascular disorders, Raynaud's syndrome, thrombo-angiitis obliterans, intermittent claudication and also as a test drug to select cases for sympathectomy.

Dose.—Tablets of 25 mg. (2/5 gr.) three times a day gradually increased to 50 mg. (3/4 gr.) four times a day. *Ampoules*, 1 mil of 10 mg.

PILOCARPINAE NITRAS

(Pilocarp. Nit.)

Pilocarpine Nitrate. $C_{11}H_{16}N_2O_2HNO_3$.—The nitrate of an alkaloid, pilocarpine, obtained from the leaves of *Pilocarpus microphyllus* and other species of *Pilocarpus*, Jaborandi leaves. In colourless crystals, or white crystalline powder. *Soluble* in 8 parts of water.



B. P. Dose.—1/20 to 1/5 gr. or 3 to 12 mg.

NON-OFFICIAL PREPARATIONS

1. **Guttae Pilocarpinae, B.P.C.**—Pilocarpine Nitrate 0.91 p.c.
2. **Pilocarpine Hair Lotion.**—Pilocarpine Nitrate 2 grs., Quinine Hydrochloride 8 grs., Glycerin 2 drs., Tinct. Cantharidin. 1 dr., Aqua Rose 5 drs.

PHARMACOLOGY

Pilocarpine is directly antagonistic to atropine in its effects upon the secretory nerves, the ends of the nerves governing the involuntary muscles, the ends of the vagus, and the ends of the third nerve in the eye. These effects are due to parasympathetic stimulation and will act even after the nerves are divided and allowed to degenerate.

Eyes. (*a*) *Pupil.*—Locally applied or given by the mouth or subcutaneously, it causes **contraction of the pupil.** This effect, which is prevented by the previous use of atropine, is due to stimulation of the myoneural junctions of the oculo-motor nerve, and observed even after the nerves have degenerated. There is no stimulation of the sphincter muscle itself. It increases the flow of tears.

(*b*) *Accommodation.*—The ends of the third nerve in the ciliary muscle are stimulated, causing bulging of the lens and fixation of the eye in accommodation for near objects.

(*c*) *Intra-ocular tension.*—After a momentary rise the tension is diminished. This coincides with the contraction of the pupil and results from the increased escape of fluids which follow the opening of the spaces of Fontana.

Internally.—Pilocarpine readily enters the circulation and is carried to different structures, where it produces definite effects, which are described below.

Salivary secretion.—Within about ten minutes after administration, pilocarpine produces a copious secretion of saliva of almost normal composition by directly stimulating the parasympathetic (cholinergic) endings of the chorda tympani and the glosso-pharyngeal in the glands.

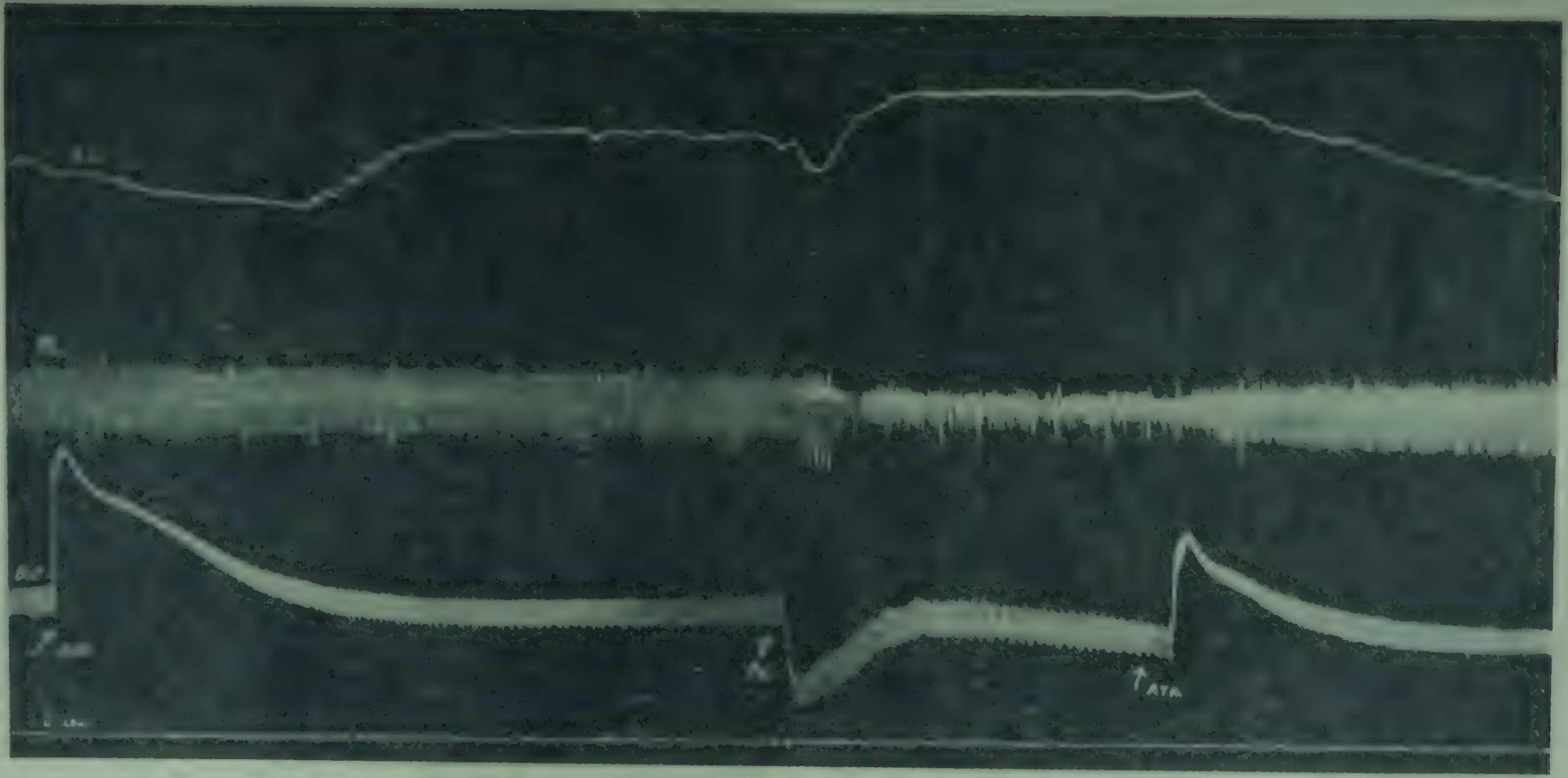


Fig. 10.—Dog. Showing effect of Adrenaline, Pilocarpine and Atropine on blood pressure, respiration and intestinal contraction.

Note the rise of blood pressure and relaxation of the intestine with adrenaline : fall of pressure, spasm of bronchial muscles and increased intestinal contraction with pilocarpine. All these effects are antagonised by atropine, i. e. it causes rise of pressure, relaxation of the bronchial muscles and of the intestine.

It is therefore a **powerful sialagogue**, the secretion amounting to a pint and a half, after one injection. The salivation is stopped by injection of atropine.

Alimentary system.—The peristaltic movements of the unstriped muscles of the gastro-intestinal canal are increased by large doses owing to direct stimulation of the parasympathetic endings of the vagus, causing nausea, vomiting, colicky pain and diarrhoea. The gastric juice and intestinal secretion are also increased. The biliary secretion is unaffected, but the spleen contracts. The pancreatic secretion is slightly affected, possibly due to muscular contraction of the duct, or indirectly through increased gastric secretion.

Skin.—Within six to ten minutes after a hypodermic injection of pilocarpine nitrate ($\frac{1}{4}$ to $\frac{1}{2}$ gr.) the face, neck and ears become flushed and drops of perspiration appear upon them, soon extending over the whole surface. The sweating is so profuse as to soak garments and bed clothes ; about 2 to 3 litres of sweat may thus be excreted by one diaphoresis. Pilocarpine therefore is a **powerful sudorific.** This effect is antagonised by atropine. Although the sweat glands are innervated by the sympathetic fibres, these functionally act as parasympathetic and are cholinergic in their effects.

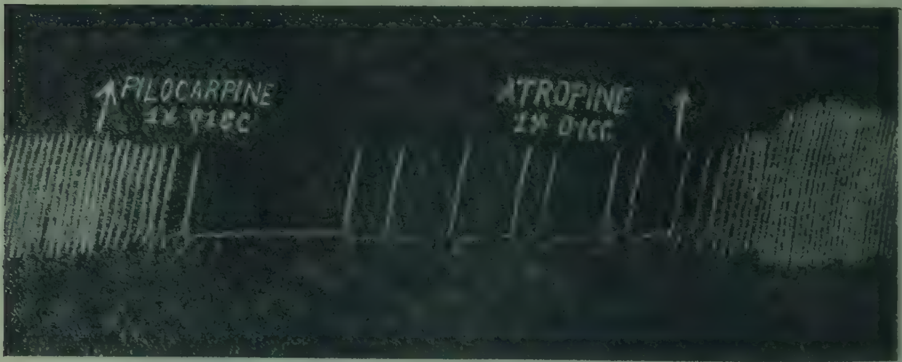


Fig. 11.—Tracing of the movements of the Isolated Rabbit's Heart perfused with oxygenated Ringer-Locke solution.

At the 1st arrow a small dose of Pilocarpine was added to the fluid, at 2nd arrow this was replaced by atropine. Note the depressant effect of pilocarpine—prolongation of diastole and slowing of the rate : atropine completely antagonises the action.

Circulatory system.—Both the heart and pulse are accelerated at first, but are soon slowed and depressed. Quickening is the usual therapeutic effect when pilocarpine is given by the mouth. The effect on circulation is variable and depends on several factors, e.g. the dose and species of animal. When a large dose is given directly into the circulation the vagal effect becomes marked and the heart is slowed with fall of blood pressure. Atropine

counteracts the slowing of the pulse, thus showing that pilocarpine depresses the heart by stimulating parasympathetic endings of the vagus. It also depresses the heart directly, therefore the margin of safety is small. The vessels of the body specially those of the head and neck dilate and the blood pressure falls from depression of the vaso-motor centre and the heart, though there may be a rise at first from vaso-constriction due to some liberation of adrenaline and contraction of the vessels of the splanchnic area. In toxic doses there is vaso-motor paralysis.

The number of white blood corpuscles (lymphocytes) is increased from contraction of the spleen muscles.

Respiratory system.—Pilocarpine increases both the nasal and bronchial secretions, and owing to the increased contraction of the bronchial muscles the breathing may be laboured and the amount of air entering and leaving the lungs is diminished. The respiratory centre is not affected directly by small quantities of pilocarpine, but the circulatory changes diminish the amount of blood passing through the lungs. These effects combined with circulatory depression tend to promote oedema of the lungs, asphyxia, collapse and death.

Urinary tract.—Pilocarpine has no effect on the secretion of the urine, in fact the great loss of fluid by other channels causes a decrease in the amount of urine. Large doses given repeatedly produce glycosuria and diuresis probably by increasing the renal permeability. By its contractile effect on the bladder it causes suprapubic pain and irresistible desire to pass water.

Female generative organs.—Pilocarpine causes the uterine muscles to contract, sometimes to such an extent as to cause abortion. It also increases uterine and vaginal mucus. The secretion of milk is not affected, although earlier investigators claimed for it a galactogogue action. It is evident that the mammary glands do not possess any true secretory nerves.

Summary of action.—It will be observed that pilocarpine performs two most important specific functions, viz. :—(1) *Stimulation of secretion*, and (2) *contraction of the involuntary muscular fibres* due to stimulation of the nerve-endings and not to that of the muscular fibres themselves. *Salivation, diaphoresis* and *myosis* are the most marked effects. Children are less affected than adults.

THERAPEUTICS

Externally.—To promote the growth of hair, pilocarpine is largely employed in the form of hair lotion. In ophthalmic practice, it has been locally applied in iritis,

retinitis, detachment of the retina, glaucoma, etc., but it is less active than physostigmine, and its effects more transitory.

Internally.—Pilocarpine is used for its diaphoretic action in **uraemia** and **uraemic convulsions.** It is however now recognised that in uraemia poisons other than urea are responsible for the untoward symptoms, and the beneficial effect is due more to the improvement of circulation following removal of fluid which impairs kidney circulation, than to the elimination of the poison *via* the skin. It is of special service in **nephritis.** Under these conditions it promotes perspiration and secures functional rest to the kidneys and lowers blood pressure. Its use is often followed by weakness, languor, and general depression which may counterbalance any improvement following its use. The diaphoresis can be helped by wrapping the patient in warm blankets and giving him warm drinks.

Caution.—Sometimes alarming prostration and collapse may follow the hypodermic injection of 1/4 gr.; and atropine should at once be injected. It should be used with caution in valvular disease of the heart, fatty heart, emphysema and pleurisy, and the patient watched. It is contra-indicated in renal diseases associated with oedema of the lungs, as by increasing bronchial secretion it may add to respiratory distress. Children are less affected than adults.

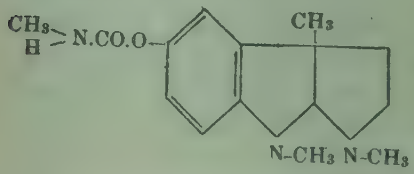
(a) Anti-choline esterase drugs

PHYSOSTIGMINAE SALICYLAS

(Physostig. Salicyl.) $C_{15}H_{21}O_2N_3,C_7H_6O_3$.

Syn.—Eserine Salicylate.

Source.—Physostigmine Salicylate is the salicylate of an alkaloid, physostigmine, obtained from the seeds of *Physostigma venenosum,* Calabar bean.



Characters.—Colourless, or faintly yellow, crystals, gradually acquiring a red tint on exposure to light and air. *Soluble* in about 100 parts of water, more soluble in alcohol (90 p.c.).

B. P. Dose.—1/100 to 1/50 gr. or 0.6 to 1.2 mg.

Official Preparations

1. **Lamella Physostigminae.**—Contains 1/1000 gr. (0.065 mg.) of physostigmine salicylate in each.
2. **Oculentum Physostigminae.** *Syn.—Oculentum Eserinae.*—Contains 0.125 p.c.
3. **Injectio Physostigminae Salicylatis.—B. P. Dose.—1/100 to 1/50 gr. or 0.6 to 1.2 mg.** N. B. When no strength is mentioned, 1/100 gr. in 15 ms. should be dispensed.

Pharmacology

The action of physostigmine resembles pilocarpine and though like pilocarpine it acts through the cholinergic fibres, its effects are not so powerful on the secretory glands; on the other hand its action on the involuntary muscles is more marked. Its action however is different from pilocarpine, and it will not act after the nerve has been cut and degenerated. Since acetylcholine which is liberated at the nerve terminals is rapidly hydrolysed, it

has been suggested that physostigmine prevents this inactivation by the ferment choline esterase in the blood and tissues, therefore it does not act after the nerve is cut and degenerated since no acetylcholine is formed. By preventing inactivation of acetylcholine, physostigmine will elicit in an intensive manner all the characteristic actions of acetylcholine. Thus it will not only produce the muscarine-like effect but also the nicotine action on the autonomic ganglia and the skeletal muscles. This is evident in the cardio-vascular response. Thus while on the one hand acetylcholine acting on the heart and blood vessels will tend to cause bradycardia, vaso-dilatation and fall of blood pressure, the same property of the drug acting on the sympathetic ganglia will cause opposite effects, i.e. quickening of the heart, vaso-constriction and rise of blood pressure. It is possible that it has some direct action on the involuntary muscles. Physostigmine also increases the amount of adrenaline secreted in the blood, and this may to a certain extent complicate its action.

Eye.—Applied locally to the conjunctiva, physostigmine is absorbed and produces the following changes—(1) **contraction of the pupil** by stimulating the oculo-motor nerve-endings ; (2) **accommodation** for near objects due to the contraction of the ciliary muscle; (3) **diminished intra-ocular tension** due to the contraction of the pupil facilitating the escape of the fluid by allowing it freer access to the spaces of Fontana.

Physostigmine fails to produce contraction of the pupil after degeneration of the third nerve, although the muscle of the iris is intact and can be made to respond to electrical stimulation or other drugs.

Internally. **Mouth.**—Physostigmine **increases the salivary secretion** since the glands are under parasympathetic control, but this is less than pilocarpine and is antagonised by atropine.

Stomach and intestines.—It is readily absorbed by the stomach and increases the gastric and intestinal movements by stimulating the vagal endings. In therapeutic doses the peristaltic movements become more active, consequently there may be vomiting, and since the intestinal contents are hurried down, there is diarrhoea with watery stools.

Heart and circulation.—The effect on the heart and blood vessels as explained above is varied and depends on several factors. In man the nicotine effect on the cardiac sympathetic ganglia counteracts to some extent the muscarine action so that slowing of the rate and lowering of the blood presure is not observed, on the other hand secretion of adrenaline produces vaso-constriction, tachycardia and rise of pressure.

The **blood pressure** rises from the increased contra tion of the heart aided partly by (*a*) the contraction of t arteries by the direct stimulation of the arterial nerv endings, and partly by (*b*) the tetanic contraction of t intestinal tract thus expelling the blood from the mese teric area. This action is therefore independent of t vaso-motor centre, for it is not prevented by section of t cord or the splanchnic nerves.

Respiration.—This is at first quickened but soon d pressed. The acceleration is caused (1) by the stimu tion of the respiratory centres of both the medulla and t cord ; (2) by the stimulation of the peripheral termi tions of the vagus in the lungs ; and (3) by the spasmo contraction of bronchial tubes producing partial asphyx Death takes place from failure of the respiratory centr

In th. dose **Nervous system.**—The motor cerebral cortex becom more excitable causing epileptiform convulsions ; the have been attributed to partial asphyxia caused by res ratory paralysis and bronchial constriction. In large dos it depresses the central nervous system beginning fro the cord and spreading upwards with diminished refl excitability. The consciousness is not affected even toxic doses, and the mind remains clear to the last. T pupils may be contracted, but not as a rule to any gre extent. The respiratory centre is stimulated first.

Muscles.—In normal persons therapeutic doses ha little effect on skeletal muscles but large doses cause fibr lary contraction. This is due to the preservation of acet choline normally present at nerve-endings of the striat muscles, for it takes place when the nerves have be divided, but disappears if the motor nerve-endings a paralysed by curare but not by atropine and does not occ after the nerve ends have degenerated. The senso nerves remain unaffected. The involuntary muscles almost every organ such as the stomach, intestines, bro chioles, bladder, heart, arteries, spleen, uterus, iris, et are stimulated producing powerful contraction.

Secretions.—Not only saliva, but sweat, tears a buccal mucus are increased in much the same way as w pilocarpine but the action is not so powerful. The sec tion of adrenaline is also increased. The secretion of mi bile and urine is not affected.

Elimination.—Physostigmine is partly excreted by t liver and salivary glands, and by the kidneys. Most it is destroyed in the tissues.

Antagonists.—Atropine, chloral and strychnine.

Toxicology.—Poisoning by physostigmine is rare. Emetics pump. Stomach wash with 0.2 p.c. potassium permanganate. A pine 1/30 gr. hypodermically till the pupils dilate well. Strych if necessary. Artificial respiration overcomes respiratory trou.

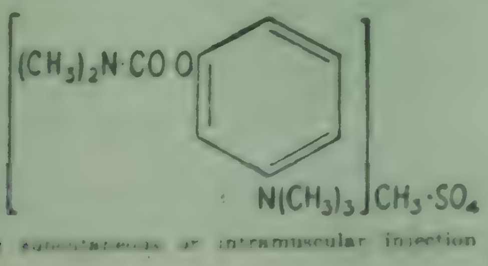
THERAPEUTICS

Eye.—Eserine is chiefly used (1) to contract the pupil in photophobia, and diminish the amount of light falling on a sensitive retina ; (2) to break up adhesions in iritis ; (3) to prevent prolapse of the iris after corneal wounds, ulcers or perforation ; (4) to reduce intra-ocular tension in glaucoma and perforating keratitis ; (5) to stimulate the paralysed ciliary muscles and iris ; (6) in detachment of the retina ; and (7) to antagonise the effects of atropine, homatropine and cocaine on the pupil. It is generally used in $\frac{1}{2}$ to 1 p. c. solution, 2 to 4 drops being dropped into the eye at a time.

Internally.—For its depressing effect on the central nervous system it has been used in several convulsive diseases, chiefly tetanus, chorea, etc., but without any appreciable benefit. As it increases intesinal peristalsis its use has been extolled in atony of the intestine, tympanites, post-operative intestinal paralysis, and chronic constipation. In all these conditions it is administered subcutaneously ($\frac{1}{60}$ gr.).

On the assumption that acetylcholine is the chemical transmitter of the impulse at the motor nerve-endings to the skeletal muscles, it has been suggested that in diseases characterised by paresis of the skeletal muscles there might be insufficient formation or rapid destruction of acetylcholine formed in response to a nervous impulse. Physostigmine has therefore been used in the treatment of **myasthenia gravis** on the idea that it will prevent the destruction of acetylcholine and intensify the action of the transmitter. For this purpose it has been used in doses of [illegible] to [illegible] gr. by the mouth in an empty stomach or hypodermically, but the results have not been very encouraging because of its general stimulating effect on the parasympathetic system. It has therefore been replaced by neostigmine, or used with atropine $\frac{1}{100}$ gr. It has also been used in hemiplegia and other forms of paralysis.

NEOSTIGMINAE METHYLSULPHAS. (Neostig. Methylsulph.). **Syn.**—**Prostigmin.**—Neostigmine Methylsulphate is the dimethyl carbamic ester of 3-hydroxyphenyltrimethylammonium methylsulphate. In white crystalline powder. Odourless ; taste, bitter. Soluble in about 10 parts of water, less soluble in alcohol (90 p.c.).



B. P. Dose. By subcutaneous or intramuscular injection : 1/120 to 1/30 gr. or 0.5 to 2 mg.

Official Preparation

1. **Injectio Neostigminae Methylsulphatis.**—B. P. Dose.—By subcutaneous or intramuscular injection : 1/120 to 1/30 gr. or 0.5 to 2 mg. N. B. If the strength is not mentioned, 1/120 gr. in 15 ms. should be supplied.

Neostigminae Bromidum.—$C_{12}H_{19}O_2N_2Br$. **Syn.**—Prostigmin.—Neostigmine Bromide is the dimethylcarbamic ester of 3-hydroxy phenyltrimethylammonium bromide.

Characters.—A white, crystalline powder ; odourless ; taste, bitter. Soluble in about 1 part of water, and in alcohol (90 p.c.).

B. P. Dose.—1/6 to 1/3 gr. or 10 to 20 mg.

Action and Uses

Neostigmine is a synthetic preparation introduced under the trade name of "Prostigmin." Its action resembles physostigmine with this difference that it has a more powerful action on the intestine and little on the eye, and none on the circulation. It acts both on the parasympathetic nerve endings in smooth muscle and the end-plates in striated muscle by preventing destruction of acetylcholine at the nerve endings by choline esterase. The effect on the smooth muscle is antagonised by atropine and on the striated muscle by curare and to some extent by quinine.

Neostigmine therefore is used in all conditions of paresis of both voluntary and involuntary muscles, e.g. in **postoperative intestinal paresis**, constipation due to atony of the intestine and in retention of the urine. It has been used in **myasthenia gravis** with good results in 1/4 gr. (15 mg.) doses by the mouth in the form of tablets, and is often combined with atropine to counteract the undesirable effects when large doses are used. It has been recommended to expel abdominal gas in X-ray examination, in delayed menstruation and as an early test for pregnancy. For this purpose it is given in three successive days 1 mil. of 1 in 2000 solution hypodermically. If menstruation does not follow pregnancy is present. It is not a satisfactory test. Used in Raynaud's disease and to potentiate morphine when only half the dose of morphine will relieve pain.

2. Drugs Depressing the Parasympathetic endings

BELLADONNAE HERBA

(Bellad. Herb.)

Syn.—Belladonnae Folium ; Belladonna Leaf ; Deadly Nightshade Leaves.

Source.—Belladonna Herb consists of the leaves, or leaves and other aerial parts, of *Atropa Belladonna* Linn., or *Atropa acuminata* Royle ex Lindley, or a mixture of both species, collected when the plants are in flower, and dried. Contains not less than 0.3 p.c. of the alkaloids of Belladonna Herb, calculated as hyoscyamine.

Composition.—(1) *Atropine*, (2) *Hyoscyamine*, (3) *Belladonnine*, **minute quantities.**

Belladonnae Herbae Pulvis. (Bellad. Herb. Pulv.).—Powdered Belladonna Herb.

Belladonna Praeparata. Syn.—*Pulvis Belladonnae ; Powdered Belladonna Leaf.*—Prepared Belladonna Herb is belladonna herb, reduced to a fine powder and adjusted, if necessary, either by the admixture in suitable proportions of powdered Belladonna Herb, having a lower or higher alkaloidal content, or by the addition of powdered exhausted Belladonna Herb, to contain 0.3 p.c. of alkaloids calculated as hyoscyamine.

B. P. Dose.—1/2 to 3 grs. or 30 to 200 mg. Contains 1/100 gr. hyoscyamine in 3 grs.

Note.—When Belladonnae Herba, Belladonnae Folium, Pulvis

Belladonnae Herbae or Pulvis Belladonnae Folii is prescribed. Belladonna Praeparata shall be dispensed.

Official Preparations

1. **Extractum Belladonnae Siccum.**—Alkaloid 1 p.c. or 1/100 gr. in 1 gr. B. P Dose.—1/4 to 1 gr. or 15 to 60 mg.
2. **Tinctura Belladonnae.**—Contains 0.03 p.c. w/v of the alkaloids, of belladonna herb, calculated as hyoscyamine, or 1/200 gr. in 15 ms. B. P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

BELLADONNAE RADIX. (Bellad. Rad.).—Belladonna Root is the dried root, or root and rootstock of *Atropa Belladonna* Linn., or of *Atropa acuminata* Royle ex Lindley, or a mixture of both species. It contains not less than 0.40 p.c. of the alkaloids of belladonna root calculated as hyoscyamine.

Composition.—The same as that of the herb (*see above*).

Belladonnae Radicis Pulvis. (Bellad. Rad. Pulv.).—Powdered Belladonna Root. Grey to light brown.

Official Preparations

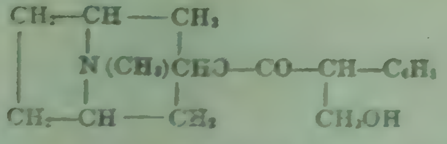
1. **Extractum Belladonnae Liquidum.**—0.75 p.c. of the alkaloids of the root calculated as hyoscyamine.
2. **Linimentum Belladonnae.**—Alkaloids 0.375 p.c.
3. **Suppositoria Belladonnae.**—Alkaloids 1/60 gr. (1 mg.) in each; or 2½ ms. of the liquid extract.

Non-official Preparation

1. **Collodium Belladonnae.** *Syn.*—*Empl. Belladonnae Fluidum.*—Liquid extract 50, Canada balsam 4, castor oil 2, camphor 1.5, pyroxyline 25, alcohol (90 p.c.) 10, ether to 100.

ATROPINA. (Atrop.). $C_{17}H_{23}NO_3$.—Atropine is an alkaloid, *dl*-hyoscyamine, obtained from *Atropa Belladonna*, *Hyoscyamus muticus*, and other plants of the family Solanaceae.

Characters.—In colourless crystals, odourless. *Solubility.*—1 in 500 of water, freely in alcohol (90 p.c.), chloroform and in 60 parts of solvent ether. The solution is *alkaline*.



Atropinae Sulphas. (Atrop. Sulph.).—Atropine Sulphate is the sulphate of the alkaloid, atropine.

Characters.—In colourless crystals, or white crystalline powder; odourless. *Solubility.*—In less than 1 part of water, 1 in 4 of alcohol (90 p.c.). The solution is *neutral*.

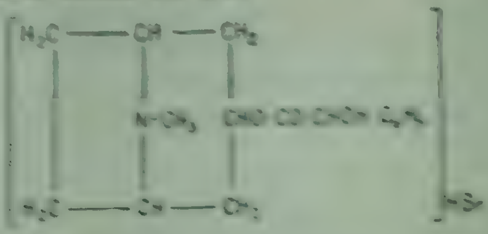
B. P. Dose.—1/240 to 1/60 gr. or 0.25 to 1 mg.

Official Preparations

1. **Injectio Atropinae Sulphatis.**—B. P. Dose.—1/240 to 1/60 gr. or 0.25 to 1 mg. N.B.—When no strength is stated, 1/100 gr. in 15 ms. should be dispensed.
2. **Injectio Morphinae et Atropinae.**—B. P. Dose.—8 to 15 ms. or 0.5 to 1 mil. Contains 1/160 gr. atropine sulphate and 1/6 gr., morphine sulphate in 15 ms.
3. **Lamellae Atropinae.**—Each contains 1/5000 gr. (0.013 mg.).
4. **Oculentum Atropinae.**—0.25 p.c.
5. **Oculentum Atropinae cum Hydrargyri Oxido.**—Atropine sulphate 0.125 p.c. yellow mercuric oxide 1 p.c.
6. **Tabellae Atropinae Sulphatis.**—B. P. Dose.—1/240 to 1/60 gr. or 0.25 to 1 mg. N. B.—If the quantity to be contained in a tablet is not stated, 1/100 gr. tablet shall be dispensed or supplied.

HOMATROPINAE HYDROBROMIDUM. (Homatrop. Hydrobrom.). $C_{16}H_{21}NO_3 \cdot HBr$.—Homatropine Hydrobromide is the hydrobromide of an alkaloid, homatropine, prepared from tropine and mandelic acid.

Characters.—A colourless crystalline powder; [illegible]. Soluble in [illegible] of water, in [illegible] parts of alcohol (90 p.c.).



Official Preparation

1. **Lamellae Homatropinae.**—1/100 gr. (0.65 mg.) in each.

Non-official Preparations and Derivatives

1. **Atropinae Methonitras. B.P.C.** *Syn.*—*Eumydrine.*—In white soluble crys obtained by the action of silver nitrate and atropine methyl bromide. Valu antispasmodic and less poisonous than atropine. Used with success in conge pyloric stenosis. A powerful mydriatic in 1 to 2 p.c. solution. *Dose*—1/60 to 1 gr. or 1 to 2 mg.
2. **Oculentum Atropinae et Cocainae. B.P.C.**—Atropine sulphate 0.25 p.c. a cocaine hydrochloride about 0.25 p.c.
3. **Euphthalmine.**—A synthetic compound. A 5 to 10 p.c. solution dilates t pupil like homatropine but its effects are not so lasting.
4. **Guttae Homatropinae. B.P.C.**—Homatropine hydrobrom. 8 gr., sod. ch 2½ gr., solution of eye-drops to 1 oz.
5. **Guttae Cocainae et Homatropinae. B.P.C.**—Cocaine hydrochlor. 4 gr., hom tropine hydrobrom. 4 gr., sod. chlor. 2½ gr., solution of eye-drops to 1 oz.

Pharmacology

Belladonna stimulates the brain and the vital medullar centres; depresses the sensory nerve-endings; motor nerv endings in the smooth muscles; secretory nerve-endings third nerve in the eye; and the vagus endings. Althoug it is described as acting by depressing the postganglion terminations of the parasympathetic nerves, it acts direct on the cells or peripheral receptors by preventing thes being acted upon by **acetylcholine.** It renders tissues i sensitive to muscarine effect and not the nicotine effect **acetylcholine.**

Externally.—The unbroken skin absorbs the alkalo of belladonna if combined with alcohol, chloroform, glycer or fat. Exposed mucous surfaces and raw skin absorb the more rapidly. Both belladonna and atropine powerful paralyse the peripheral terminations of the sensory nerv especially if there is pain, and are therefore **local anaesthe tics** and **anodynes.** To a much less extent they paraly the motor and secretory nerve-endings. The blood vesse of the part first contract and then dilate.

Internally.—Atropine chiefly affects the parasympath tic nervous system; other organs and tissues are indirect influenced through its action on their special or secreto nerves.

Nervous system.—Its effects on the central nerv system are those of general stimulation. But it acts mo powerfully on the higher divisions of the nervous axis, that in cases of poisoning the symptoms are referred mai

to the brain, and consist in increased co-ordinated movements like delirium and talkativeness, whereas with strychnine, which also stimulates the central nervous system, the symptoms arise from stimulation of the lower axis of the nervous system and consist of exaggerated reflexes and convulsions.

1. *Cerebrum.*—In small doses belladonna scarcely produces any effect on the convolutions, but in large doses, it stimulates the central motor area causing general nervous excitement, talkativeness, mental hallucination, disordered gait and vision. The conjunctiva and face become flushed, pulse is quickened and respiration rendered frequent. Still larger doses aggravate the symptoms causing delirium and convulsion followed by stupor and coma. The reflexes become more active but the higher psychical faculties are not affected like caffeine.

2. *Medulla and cord.*—Two chief centres are powerfully stimulated by atropine in therapeutic doses, *viz.*, (*a*) the respiratory; and (*b*) the vaso-motor. The vagal

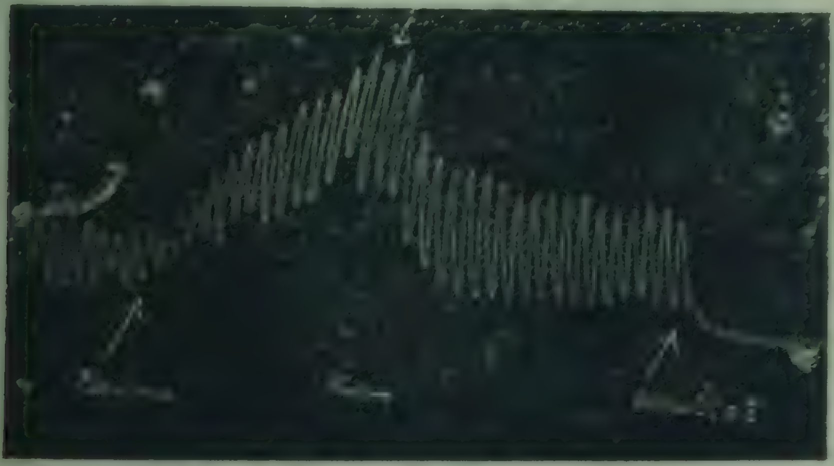


Fig. 13.—Movements of the isolated intestine.

At first arrow pilocarpine was given, note powerful contraction of the longitudinal muscles; at second arrow atropine was added when the contractions became [illegible] with normal pendulum movements; at third arrow adrenaline was given; note complete relaxation of the muscles.

centre is affected in small doses. It also slightly increases and then diminishes the reflex excitability.

3. *Sensory nerves.*—Belladonna, whether locally applied or given by the mouth, paralyses the peripheral terminations of the sensory nerves and thereby relieves pain if present. It is therefore a local and general anodyne.

4. *Motor nerves and voluntary muscles.*—The motor nerves are slightly paralysed towards the end, but the voluntary muscles are never affected.

5. *Stomach and intestine.*—In the stomach atropine

relieves pyloric spasm, without interfering with the norma movements of the stomach, when due to vagus stimulatio but not when the sympathetic is concerned (Sollmann) In ordinary therapeutic doses the normal movements o the intestine are not influenced nor the effects of purga- tives interfered with, *i.e.* it does not interfere with peris- talsis, but relieves the griping pains and irregular move- ments of the gut by depressing the vagal endings.

Atropine inhibits the movements of the isolated strips of intestine and will antagonise the action of pilocarpine due to its depressing effect on the parasympathetic nerve- endings.

6. *Bladder urethra, uterus, etc.*—The termination of the nerves supplying the involuntary muscles of the bile duct, bladder, ureter, vesiculae seminalis, uterus, vagina are paralysed. Atropine therefore relieves spasm of these organs, and in cases of bile duct and ureters help passage of calculi.

7. *Third nerve in the eye.*—Atropine has the follow- ing important effects on the eye ; (*a*) *The pupil.*—Atro- pine administered internally **dilates the pupils** and when dropped into one eye it dilates the pupil of that eye, but has no effect on the other eye. Dilatation is due to the paralysis of the parasympathetic endings of the third nerve, and since the direct stimulation of the sphincter iridis results in contraction it has no effect on the muscle. There is also loss of light reflex.

(*b*) *Accommodation.*—Atropine paralyses the termi- nations of the third nerve in the ciliary muscle (the ante- rior surface of the lens becomes flatter) and thus **paralyses accommodation,** the eye being focused for distant object. It is therefore strongly cycloplegic.

(*c*) *Intra-ocular tension.*—As an indirect result of the dilatation of the pupil by which the flow of lymph is obstructed, atropine **increases intra-ocular tension.**

8. *Vagal endings in the heart.*—Atropine in small doses 0.5 to 0.6 mg. ($\frac{1}{120}$ to $\frac{1}{100}$ gr.) **stimulates the vagus centre** causing slowing of the pulse. But when large doses ($\frac{1}{75}$ gr.) are given, or small doses repeated, then quicken- ing of the rate is observed due to depression of the vagal nerve-endings. This quickening cannot be diminished by stimulating the vagus. With the acceleration of the pulse atropine does not reduce the force and tone of the heart. Since the inhibitory fibres are almost inactive at birth, atropine has no effect in increasing the heart beat in the new born child. It has also little effect in old age. The vagus effect shows both at the sinus and the auriculo- ventricular nodes, and atropine therefore checks heart- block caused by digitalis.

9. *Vagal endings in the bronchial walls.*—Both the

afferent and efferent terminal filaments of the vagus are paralysed producing relaxation of the bronchial muscle. and diminish the sensibility and reflex action (paralysis of the afferent fibres). These are the only effects produced in therapeutic doses. Thus atropine is a **bronchial antispasmodic.** The sympathetic fibres which dilate the **bronchi are unaffected.**

In large doses the respiration becomes quicker and deeper from stimulation of the respiratory centre and increased formation of CO_2, but toxic doses paralyse it and **make it shallow and slow.**

10. *Vaso-motor nerves and the skin.*—The action of belladonna on the blood pressure depends on its effect on the heart. After a temporary fall the pressure rises above normal partly from its effect on the heart and partly from stimulation of the vaso-motor centre. The rise of blood pressure is greater if it has been lowered by excessive vagus stimulation of the heart and dilatation of the blood vessels (*see* Fig. 10 p. 239). In toxic doses the vaso-motor centre is paralysed and the blood pressure falls. The arteries of the skin, especially those of the head and neck, are dilated in toxic doses giving rise to flushing of the face, or scarlatiniform or erythematous rash on the skin so often seen in belladonna poisoning. Some patients are specially susceptible to belladonna and a single therapeutic dose causes **flushing of the skin and dryness of the** mouth. This is due to **idiosyncrasy.**

11. *Secretory nerves.*—Most of the secretions, namely, salivary, gastric, pancreatic, mucous glands in the whole alimentary canal and respiratory passages and sweat are diminished, due not to any direct effect on the secretory cells but by preventing the effect of nerve impulse, *i.e.* renders the cells insensitive to acetylcholine. It has no action on the secretion of bile, milk and urine.

(*a*) *Salivary and mucous glands.*—Atropine paralyses the terminations of the secretory fibres of the chorda tympani, but not the vaso-dilator ones, so that stimulation of the chorda tympani, does not increase the flow of saliva from the submaxillary gland though its vascularity is increased. Stimulation of the sympathetic still induces secretion, showing that although the secretory nerves are paralysed secreting cells are not influenced in any way. It also depresses the terminations of the secretory nerves of other salivary and mucous glands. Consequently, the mouth, palate and throat become dry and red. After large doses the dryness increases so much that deglutition becomes impossible. Hence atropine is a powerful **antisialagogue.**

(*b*) *Gastro-intestinal glands.*—No effect on gastric secretion is observed when atropine or belladonna is given

orally in small doses, but large doses, specially when ad-
ministered hypodermically, paralyse the terminations of
the secretory fibres of the vagus in the stomach, and reduce
or even arrest the gastric secretion. The hydrochloric
acid is more reduced than pepsin or the fluid as a whole.

(*c*) *Liver and pancreas.*—Secretion of the pancreas
depends upon the presence in the blood of secretin rather
than on nerve impulse, and since atropine reduces the
secretion of hydrochloric acid in the stomach which in the
duodenum acts as stimulant to the formation of secretin
there is some diminution in the secretion of the pancreatic
juice. The secretion of bile is little affected by atropine.

(*d*) *Bronchial glands.*—The secretion of the bron-
chial and tracheal mucus is very much diminished.

(*e*) *Sweat glands.*—Atropine powerfully checks
sweating by paralysing the terminations of the sympathe-
tic nerves (cholinergic), in the sweat glands. The skin
therefore becomes dry and hot. Applied locally it has no
influence over the secretion of the sweat.

(*f*) *Mammary glands.*—The secretion of milk is not
arrested since the secretion is largely independent of the
nervous system.

(*g*) *Lachrymal glands.*—Prolonged use of atropine
arrests their secretion.

(*h*) *Kidneys.*—Since the kidneys are not controlled
by any secretory nerves, atropine has very little effect on
the amount of urine. Large doses cause retention of urine
as the result of paralysis of the bladder.

Temperature.—Belladonna in moderate doses raises
the temperature of the body by 3 to 4 degrees due possibly
to suppression of perspiration. As the circulation fails
the temperature falls.

Clearance.—It is partly oxidised in the body possibly
in the liver, the unoxidised portion is excreted by the urine
within 10 to 20 hours. Part of it may be broken up into
tropine. Traces have been found in the milk.

Toleration.—Children can bear large doses of bella-
donna. Old people bear it badly but some tolerance may
be produced by the gradual increase of dose. *Idiosyncrasy*
to the drug is common, some patients showing flushing,
dryness of the mouth and throat and an erythematous
rash even with ordinary therapeutic doses. This is often
noticed amongst members of the same family, all the
members being susceptible to it.

Summary of action.—1. Atropine stimulates the
following :—(*a*) Cerebrum, producing delirium ; (*b*) vital
medullary centres—respiratory, vagal and vaso-motor.
2. It depresses (*a*) the sensory nerve-endings ; (*b*) the
motor nerve-endings in the smooth muscles of the viscera,
thus allays abnormal contractions of the muscles of the

bronchi, stomach, intestine, bile duct, etc., and acts as an antispasmodic ; (c) the parasympathetic endings of the third nerve of the eye ; and (d) the vagus nerve-endings —making the heart free from the inhibitory nerve control.

Acute toxic action.—The symptoms that follow a moderate dose of atropine are (1) dry mouth and throat, (2) dilated pupil, (3) dim vision, (4) dry skin, (5) dysuria, (6) dysphagia, and (7) delirium (wild). Erythematous rashes are common. At the *post mortem* all organs are in a state of venous congestion due to asphyxia.

The symptoms of poisoning have been observed after the application of the plaster, glycerin of belladonna, or liniment.

Treatment.—Emetics or pump. Tannin, tea, charcoal ; morphine 1/6 gr. in the early stage, caffeine. Pilocarpine or physostigmine are of little value since their action is peripheral and the poisoning is dependent upon cerebral and medullary effects. Stimulants, hot bottles, artificial respiration and CO_2 and oxygen inhalation. Ice to the head for dilirium. As the poison is eliminated by the urine, the bladder should be emptied now and then to prevent reabsorption.

Therapeutics

Externally. **Skin.**—As a local **anodyne,** the liniment, plaster or ointment are largely employed to soothe irritability or pain in neuralgia, soreness of muscles, etc. Occasionally atropine injected subcutaneously as near the nerve as possible does more good in neuralgia, especially in **sciatica,** than any local application. Glycerinum belladonnae (green extract 60 p.c. with glycerin and water) or collodium belladonnae may be applied over threatening boils, abscesses, etc. In the form of an ointment either alone or better still with conium, belladonna lessens the spasm of anal fissure and the pain and irritation of **piles.**

Female diseases.—Extract of belladonna with glycerin (5 to 10 grs. to 1 oz.) in cotton wool may be used as a tampon in inflammation of the womb or cervix. A suppository containing extract 1 gr. will relieve the pain of spasmodic and neuralgic dysmenorrhoea.

Eye.—A solution of atropine is dropped into the eye to dilate the pupil to facilitate examination of the internal eye posterior to the pupil, and paralyse the accommodation in fitting glasses. Smaller doses (0.1 to 0.01 p. c. solution) will dilate the pupil but stronger solution (1 p. c.) is required to paralyse accommodation. As a rule accommodation does not recover till after 5 to 7 days, and the pupil does not become normal till after one to two weeks. Where only temporary mydriasis is required, as in estimating errors of refraction, homatropine may be used as the effects pass off more quickly and there is less likelihood of toxic effects from absorption. In inflammatory conditions it is applied to give rest to the iris and ciliary muscle, and in iritis to prevent formation of adhesions to the lens and cornea. It is contraindicated where there is suspicion of glaucoma as by increasing intra-ocular pressure it may

either aggravate the disease already present or may pre-cipitate an acute attack.

Internally.—Atropine is indicated in all condition where a depression of the parasympathetic nerve-ending is required. It is therefore used to diminish secretion o sweat, or saliva ; to reduce spasm of involuntary muscles *e. g.* of bronchi, stomach, intestine, sphincter of the gall bladder, urinary bladder and uterus ; and to stimulate th respiratory centre.

Alimentary canal.—Atropine checks excessive saliva tion from any cause. As it lessens the secretion of gastri juice and the motor activity of the stomach, atropine ma be used in hyperchlorhydria, gastric ulcer, etc., and i specially valuable in acute conditions with severe pain The extract is often combined with purgatives either to increase their activity or to lessen griping. It has been used in some form of constipation, e.g. spastic constipation

In full doses ($\frac{1}{80}$ gr.) atropine is useful in sea sickness where it acts by paralysing the vagus. In fact persistent vomiting often results from pyloric spasm which is checked by atropine.

Belladonna is often effective in **intestinal obstruction** due to faecal stasis, atony of **the intestine and reflex stric-ture** ; but to be of any use it should be given in large doses (20 to 30 ms.) frequently till the symptoms of poisoning appear. Alone or with opium it is useful in peritonitis enteritis and appendicitis. It also relieves the pain of biliary, intestinal and lead colic by paralysing the sensory nerve-terminations and relaxing the involuntary muscles and since it does not cause constipation it is preferable to morphine, specially in lead colic. In *cholecystitis* bella-donna is used to subdue reflex spasm of the gall-bladder. The tincture is better than atropine, the only point to re-member is to find out the correct dose for the particular patient. A hypodermic injection of atropine ($\frac{1}{20}$ gr.) often helps reduction of hernia or volvulus.

Heart and circulation.—Belladonna relieves palpita-tion, pain and distress of the heart. For this purpose a plaster is often applied over the cardiac region. As a pre-liminary to general anaesthesia atropine is injected sub-cutaneously to check excessive vagus stimulation. It is used in **bradycardia** or **partial heart-block**, but has no effect in complete and permanent heart-block. On the other hand when the slowness of the heart is due to disease of the muscle itself atropine is of no use. In fact its use has been suggested as a means of diagnosis between myogenic and neurogenic bradycardia. In these cases atropine must be pushed to the limit of physiological tolerance. As it has very little effect in accelerating the pulse in typhoid fever where the heart muscle is

affected by the toxin, it has been used to differentiate typhoid from other fevers. The method is to ascertain the normal pulse rate which is taken every minute until it is steady, when [illegible] gr. of atropine is given hypodermically. After 25 minutes, the pulse rate is again taken and recorded minute by minute until the temporary acceleration is over (which takes about 15 to 20 minutes). If the acceleration is within 10 per minute, the infection is probable. This test is observed in the second week and in patients not over 80 years.

Respiratory tract.—Belladonna is extremely useful **in** many spasmodic affections of the air-passages, such as asthma, spasmodic bronchitis and whooping cough. A subcutaneous injection of atropine ($\frac{1}{100}$gr.) either alone or with 0.5 mil (8 ms.) of adrenaline solution gives great relief in asthma by relaxing the bronchial spasm. In whooping cough* the tincture must be given freely before one may expect any decided improvement. In nasal catarrh with profuse discharge atropine gives immediate relief. As it stimulates respiration, atropine may be used in pneumonia and in narcotic poisoning. When used before giving volatile anaesthetic it prevents reflex vagus stimulation of the heart and reduces excessive salivary secretion, and when combined with morphine as a preliminary to ether anaesthesia it offsets the depressing effect of morphine, **or** of the anaesthetic itself, on the respiration. It however interferes with the pupillary signs of the volatile anaesthetic. It has also been used to prevent **anaphylaxis.**

Skin.—Atropine ($\frac{1}{100}$ gr. or 0.6 mg. hypodermically) arrests excessive sweating. It is therefore an excellent remedy for night sweats of phthisis.

Nervous system.—Belladonna is now rarely used in nervous diseases. It sometimes controls delirium in fevers. Atropine is used in the treatment of **post-encephalitic parkinsonism** where it gives great relief by diminishing muscular rigidity, reducing tremors, and lessening excessive lachrymation and salivation. The method consists in ascertaining the *maximum dose* that causes improvement by a daily graduated increase of dose. When such increase yields no further benefit, the dose is similarly decreased until the return of the symptoms show that the dose is too small. Begin with a total daily dose of 0.5 mg. ([illegible] gr.) in two doses and increase by 0.5 mg. daily, spread over three doses, till no further improvement

*Pot. brom.	grs. 2-4
Pot. bicarb.	grs. 2
So. ammon. aromat.	ms. 4
Tinct. bellad.	ms. 2-5
Syr. prun. serot.	ms. 15
Aqua anethi	ad. oz. 1/2

In whooping cough for child 2-4 years.

is noticed ; keep on at this maximum dose for a few da then reduce the dose by 0.25 mg. ($\frac{1}{260}$ gr.) daily unti point is reached at which subjective and objective sym toms return. A slightly higher dose than this is the *op mum dose*. In mild cases the optimum dose is 3 to 8 mg. (to $\frac{1}{8}$ gr.) daily ; in severe cases it varies from 12 to 24 m

Genito-urinary tract.—Belladonna in the form of tin ture is a useful remedy in incontinence of urine in childre By relaxing the spasmodic contraction of the sphincter the bladder, it relieves retention of urine from over-activi of the sphincter. It is very useful in allaying the pa and helping the expulsions of **renal calculus**, but in or to obtain these effects it must be given in large doses atropine may be used subcutaneously in doses of 1/60 g Cystitis, dysuria, urethral spasms and, in fact, any ki of pain in the pelvic organs, *e.g.* dysmenorrhoea, can removed by belladonna either used in the form of suppository or by the mouth.

Prescribing hints.—Atropine may be combined with morphi to counteract its unpleasant physiological effects and to increase sedative virtue. 10 ms. of the tincture every 4 hours to you children for *whooping cough* ; and 30 to 40 ms. of the same eve 1 or 2 hours during an *attack of renal colic* until atropism—dryn of the throat, dilatation of the pupils and delirium—sets in are unsafe to use in these cases.

Homatropine hydrobromide may be applied into t eye either in solution (4 grs. in 1 oz. of water), or as disc, or dissolved in castor oil with cocaine. The obje of mixing it with castor oil is to prevent it from bei washed away by the tears. As it dilates the pupil mo quickly (within an hour) and the effects are of short duration (passing off within 24 hours), it is used in pr ference to atropine, moreover it has less tendency to i crease intra-ocular tension. It is therefore a more co venient drug for examination of the eye, unless it is d sired to paralyse completely the ciliary muscles.

Atropine Substitutes (Not Official)

A number of synthetic compounds having only t antispasmodic property of atropine without its other sid effects have been introduced recently as spasmoly agents. They are largely used to relieve gastro-intestin irritability, pylorospasm, and dysmenorrhoea when due uterine hypertonicity, and also in irritability of t urinary bladder.

Syntropan.—3-diethylamino-2,2-dimethy-*l*-propanol tropate ph phate. A white crystalline powder, soluble in alcohol. An effecti antispasmodic, particularly in peptic ulcer and associated pylorospa with very slight toxic effect in comparison to atropine.

Dose.—*Oral*, 50 mg. (3/4 gr.) twice a day ; *subcutaneous intramuscular*, 10 mg. (1/6 gr.) in 1 mil. solution.

Trasentin.—Diphenylacetyldiethylaminoethanol Hydrochloride. white crystalline needles, soluble in water. In addition to its spasmolytic action it is a mild local anaesthetic and is used in the treatment of peptic ulcer or in any hypermotile condition of gastrointestinal tract.

Dose.—*Oral*, 75 to 150 mg. (1¼ to 2½ gr.) twice daily. *Intramuscular*, 50 mg.; *rectal*, 100 mg. (1½ gr.) as suppository.

Amethone.—3-(2-diethylaminoethyl)-3-phenyl-2(3)-benzofuranone hydrochloride. A crystalline powder, soluble in water. It is spasmolytic smooth muscles of many organs particularly those of the ureter and bladder.

Dose.—*Oral*, 50 to 100 mg. (3/4 to 1½ gr.) in capsule every hours; *intramuscular*, 100 mg. in 2 mils aqueous solution every hours.

Novatropine.—A homatropine methylbromide. It is a white crystalline powder, soluble in water and alcohol. Used in the treatment of peptic ulcer, pylorospasm, hyperchlorhydria and spastic colon.

Dose.—2.5 to 5 mg. (1/24 to 1/12 gr.) 2 to 3 times a day before meal; *subcutaneously* or *intramuscularly*.

Benzhexol. Syn.—Trihexyphenidyl; Artane.—It is 3-(piperidyl)-phenyl-1-cyclohexyl-1-propanol hydrochloride. It is a potent antispasmodic resembling belladonna alkaloids without their disadvantages. Introduced for the treatment of parkinsonism for relief of inertia, relaxation of spasm and reduction of tremor without production of dryness of the mouth or paralysis of accommodation. Only side effects are mental confusion and headache.

Dose.—Initial—2.5 mg. (1/24 gr.) daily increasing by this amount to a total of 10 mg. (1/6 gr.) a day in 4 doses. Senile and hepatic patients however require smaller doses.

Diethazine Hydrochloride. Syn.—Diparcol.—It is diethylaminoethyl-N-thiodiphenylamine hydrochloride. Gives symptomatic relief when administered continuously in Parkinson's syndrome and also certain other extra-pyramidal disorders. Sudden withdrawal of treatment may give rise to serious reactions.

Dose.—0.25 grm. or 4 grs. increased to 1 grm. or 15 grs.

HYOSCYAMUS

Hyoscyamus. (Hyoscy.)

Syn.—Henbane Leaves; Hyoscyami Folia.

Source.—The dried leaves or leaves and flowering tops of *Hyoscyamus niger*. Contains not less than 0.05 p.c. of the alkaloid hyoscyamine.

Characters.—Leaves vary in length up to 25 cm., mostly sessile; exstipulate, triangular-ovate or ovate-oblong, acute, sinuate, pale green. Furnished with glandular hairs particularly underneath. Branches cylindrical and glandular hairy; odour, strong; taste, bitter and slightly acrid.

Composition.—Chief alkaloids are (1) *l-hyoscyamine*. (2) *Atropine*. (3) *Hyoscine* . (4) **A poisonous oil.**

Incompatibles.—Liquor potassae, lead acetate, silver nitrate, vegetable acids.

Hyoscyami Pulvis.—Powdered Hyoscyamus.—Green or greyish-green.

Official Preparations

1. Extractum Hyoscyami Liquidum. Contains 0.05 p.c. w/v of the alkaloid hyoscyamine, or 1/20 gr. in 6 ms. B. P. Dose.—3 to 6 ms. or 0.2 to 0.4 mil.
2. Extractum Hyoscyami Siccum. Syn.—Extractum Hyoscyami.—0.3 p.c. of alkaloid, hyoscyamine, or 1/330 gr. in 1 gr. B. P. Dose.—1/4 to 1 gr. or 16 to 60 mg.
3. Tinctura Hyoscyami. Contains 0.005 p.c. w/v of the alkaloid hyoscyamine, or 1/200 gr. in 60 ms. B. P. Dose.—30 to 60 ms. or 2 to 4 mils.
4. Pilula Colocynthidis et Hyoscyami.—12.5 p.c. of dry extract hyoscyamus. B. P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.

Pharmacology

Hyoscyamine, the principal alkaloid in hyoscyamus,

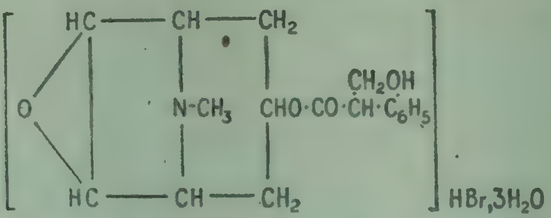
is isomeric with atropine and is easily converted into th latter in the presence of a fixed alkali at the ordinary ten perature. Most of the properties of hyoscyamus mus therefore be identical with those of belladonna and stram nium. The following are however the chief points of diffe ence :—(1) Hyoscyamus, because of the presence c hyoscine, excites the brain less and has a marked and rap *sedative and soporific effect on the cerebrum.* (2) It ha also more pronounced *sedative action on the spinal cor* (3) It is also sedative to *the intestine* and is more effic cious in relieving griping and irregular contraction. (4 It is *not a powerful stimulator* of the heart. (5) It r lieves *irritation of the urinary passages*, especially th of the bladder. This it does by depressing the ends of th nerves of the mucous membrane, and controlling the spas of the muscular fibres. (6) *Intra-ocular tension* is le affected.

THERAPEUTICS

Besides its use in those cases where belladonna is i dicated, it is employed (1) to soothe cerebral exciteme and produce sleep, as in mania and insomnia ; (2) to less cardiac asthma ; (3) to correct the painful griping of pu gatives ; (4) to relieve vesical spasm in cystitis, prost titis, calculus, etc., often in combination with other urina sedatives as buchu, and the alkalies.

HYOSCINAE HYDROBROMIDUM. (Hyoscin. Hydrobrom
Syn.—Scopolamine Hydrobromide.

Source.—Hyoscine Hydrobromide is the hydrobromide of alkaloid, *l*-hyoscine (*l*-scopolamine) ; obtained from various solana ous plants.



Characters.—In colourless, transparent, rhombic crystals. Readily *soluble* water, and in alcohol (90 p.c.).

B. P. Dose.—1/200 to 1/100 gr. or 0.3 to 0.6 mg.

OFFICIAL PREPARATIONS

1. **Oculentum Hyoscinae.—Contains 0.**125 p.c. hyoscine hydrobromide.
2. **Injectio Hyoscinae Hydrobromidi.—B. P. Dose.—1/200 to 1/100 gr.** or **to 0.6 mg. N. B.** If the strength is not stated, a solution containing 1/160 gr 15 ms. should be dispensed.

PHARMACOLOGY AND THERAPEUTICS

The action of hyoscine, so far as the peripheral effe are concerned, is identical with atropine, but the centr effects are not. It paralyses the parasympathetic ner endings like atropine, but its effects are more rapid a

powerful, though of brief duration. Like atropine it *paralyses the vagal endings* in the heart, but this effect is not elicited in therapeutic doses and the pulse rate is not altered. It allays pain, dilates the pupil, and checks secretion. A solution of 1 in 500 will act as a mydriatic and paralyse accommodation but unlike atropine the effect is more rapid and passes off within 3 to 5 days. The oculentum or a 0.2 p.c. solution is used as a mydriatic in preference to atropine.

On the central nervous system it acts as a **narcotic** and has a sedative action on the convolutions producing **sleep** which lasts for 5 to 8 hours, and since the patient remains quiet for several hours afterwards it is largely employed as a narcotic in mania, insanity, delirium tremens, tetanus, etc. It has the advantage over morphine in that it acts by quieting reflex and in not producing a habit. It has however certain unpleasant side effects and produces mydriasis, cycloplegia and dryness of the mouth. For its central effects it is used in *sea sickness*, and like atropine it also relaxes the pyloric sphincter. It is also used in chorea and paralysis agitans ; in which conditions it reduces the movements and tremors ; and relieves the rigidity and muscular hypertonus in **post encephalitic parkinsonism** ($\frac{1}{150}$ gr. a day increased to $\frac{1}{50}$ gr. or more). Here it also reduces salivation and ocular crises. Because it reduces salivation and produces dryness of the mouth it should be given after meals. Its disadvantage is toxicity, the margin of safety being small.

Large doses do not necessarily produce more profound sleep, but give rise to delirium and excitement like atropine. It depresses the respiratory and vaso-motor centres, and several cases of collapse following its use are on record.

A combination of scopolamine and morphine is sometimes used for the production of **general anaesthesia.** Scopolamine hydrobromide $\frac{1}{200}$ to $\frac{1}{64}$ gr. and morphine hydrochloride $\frac{1}{4}$ to $\frac{1}{2}$ gr. is injected on the night previous to the operation, and a similar or larger dose in the morning before the operation. This usually produces deep sleep and the patient does not wake up till some hours after the operation, thus escaping the most painful period. Smaller doses may be given to produce **basal narcosis** prior to the use of volatile anaesthetics (*see* page 168). Scopolamine-morphine anaesthesia, "twilight sleep," is advocated during the second stage of labour in place of chloroform (hyoscine hydrobromide $\frac{1}{150}$ gr. with morphine sulphate $\frac{1}{6}$ to $\frac{1}{4}$ gr.). Occasionally however it causes cessation of uterine contractions and has a tendency to prolong labour, and the child may be born apnoeic. Twilight sleep sometimes makes the patient maniacal, at least temporarily.

STRAMONIUM

Stramonium. (Stramon.)

Syn.—**Stramonium Leaves.**

Source.—Dried leaves and flowering tops of *Datura Stramoniu*
and of *D. Tatula.* Contains not less than 0.25 p. c. of the alkaloi
of stramonium, calculated as *hyoscyamine.*

Characters.—Greyish-green, ovate, petiolate, 8 to 25 cm. long, unequal at base, with dentate margin and acuminate apex. Taste, saline and bitter. T leaves are minutely wrinkled.

Composition.—Contains *hyoscyamine, atropine* and *hyoscine. Daturine* is p bably a mixture of atropine and hyoscyamine.

Stramonii Pulvis.—Powdered Stramonium.—Greyish-green.

Official Preparations

1. **Tinctura Stramonii.**—Contains 0.025 p.c. w/v of hyoscyamine, or 1/120 in 80 ms. **B. P. Dose.—5 to 30 ms. or 0.3 to 2 mils.**
2. **Extractum Stramonii Siccum.**—Contains about 8/100 gr. in 8 grs. or 1 p of the alkaloids of stramonium calculated as hyoscyamine. **B. P. Dose.—1/4 1 gr. or 15 to 60 mg.** In post-encephalitic and similar conditions.—**1 to 8 grs. 60 to 500 mg.**
3. **Extractum Stramonii Liquidum.**—Contains 0.25 p. c. of the alkaloids stramonium, or 1/120 gr. in 3 ms. **B. P. Dose.—1/2 to 3 ms. or 0.03 to 0.2 mil**

Pharmacology and Therapeutics

Internally.—The action of stramonium resembl belladonna, except that it relaxes the bronchial musc more powerfully and that it may cause irregularity of t heart. It is therefore used in **asthma** either in the for of cigarettes to be smoked, as fumes for inhalation, or i ternally by the mouth in the form of tincture. Wh combined with potassium nitrate, lobelia, black tea a oil of anise it resembles the well-known *Himrod's, Blis* and *Green Mountain Cure* (*see* page 83).

Like atropine and hyoscine, stramonium also relax the increased muscle tone of the parkinsonian. It may prescribed either in the form of the tincture in doses 10 ms. up to 60 ms. or more three times daily, or the d extract may be used in the form of a pill.

Acute toxic action.—Poisoning by stramonium is fairly comm in England, and the seeds of *Datura alba* and *D. fastuosa* are larg used by the *road poisoners in India* who mix them with food, or g them to their victim to smoke, with the object of robbery. T *symptoms* are dryness of the throat, giddiness, flushing of the fa dilatation of the pupils, and a peculiar form of delirium associa with ludicrous movements followed by coma which may end in dea

Treatment.—Emetics, stomach-pump, stimulants, cold affusi artificial respiration. If much delirium, give opium, but opium less useful in these cases than atropine in opium poisoning.

Class E : Drugs acting on the Ganglia and the Motor Nerve-endi

Curara, Nicotine, Coniine, Gelsemium, Sparteine, Lobelia (*q.v.*)

CURARA. (*Not official*). *Syn.*—Urari, Ourari, Woora Woorali.—The South American arrow-poison, prepared from bark and sapwood of of *Strychnos toxifera.*

Composition.—The most important active principle is *d*-tu curarine. Also curine, which possesses a weak curariform actior the nervous system but produces other actions on the heart

blood vessels. Other related compounds are curarine, protocurarine, protocurine and protocuridine.

PHARMACOLOGY

Nervous system.—Curare paralyses the motor nerve-endings throughout the whole body whenever a sufficient quantity enters the blood stream. It antagonises the action of acetylcholine on the voluntary muscle and blocks conduction at the nerve-endings. In large doses it paralyses the autonomic sympathetic ganglia. The sensory nerves are unaffected by curare. Physostigmine, neostigmine and potassium antagonise the action of curare.

It does not prevent the formation of acetylcholine but prevents its action on the receptors on the end plates in the muscles with which it normally combines. Curare thus produces muscular relaxation. The isolation of pure alkaloid known as *d*-tubocurarine chloride was followed by its use as **muscular relaxant** in anaesthesia. Its use is indicated in intra-thoracic operations in which cautery is to be used, and in intra-abdominal operations requiring prolonged muscular relaxation. Since it has no anaesthetic or analgesic property it is generally used with light general anaesthetic. The best results are obtained with cyclopropane or nitrous oxide and oxygen with minimal trichloroethylene rather than with ether.

Two preparations are available: (1) a solution containing 20 mg. curare extract per c.c. known as *Intocostrin*. The initial dose is 3 mil. which gives sufficient relaxation of muscles lasting for over one hour in abdominal operation. Further 2 mil. may be necessary at the end of the operation. (2) Curarine chloride (tubocurarine) powder (100 mg.). This is double the strength of the other and therefore requires more care.

Duration of effect.—The paralysing effect wears off within half to one hour, slight effects in the face and eye muscles may however remain for a period of four to six hours. Its clearance depends on the liver which destroys it as also on the efficiency of the kidneys for excretion.

Dose.—When no narcotic has been used, the efficient intravenous dose is 2 to 2.5 mg. per stone of body weight. In case of general debility or in children and old people the dose is less. For an adult the usual dose with some general anaesthesia is 15 mg. *i.e.* 1 to 1.5 mg. per stone of body weight. With ether the dose is lower. The solution is injected intravenously. *Intocostrin* contains 20 units or 20 mg. of "curare extract" per mil. *One* unit of intocostrin is equivalent in potency in man to 0.3 mg. of *d*-tubocurarine chloride.

Dangers.—Since two separate substances, one for general anaesthesia and another for muscular relaxation, are used it often becomes rather difficult to judge the depth of anaesthesia. The respiration may be completely abolished, when the pulse is the only guide, though the respiration may serve as a guide by variations in its depth and frequency. The drug is destroyed and eliminated quickly, so that in case of an overdose when there is respiratory embarassment it is overcome by a short period of artificial respiration. Its chief disadvantage is the narrow margin of safety and should be used only by experienced anaesthetists.

Other Uses.—Intocostrin has been used in shock therapy, the dose being 0.5 unit per pound of body weight, intravenously, to reduce severity of convulsion which often causes fracture of the spine; in different spastic conditions, such as paralysis agitans, tremor, mutiple sclerosis and in athetoid disorders to reduce hypertonic involuntary movements and tremor. In the form of tubocurarine chloride pentahydrate its use has been revived in the treatment of tetanus to stop convulsion and muscular spasm. For prolonged

effect (18 to 24 hours) it is used as suspension of peanut oil an beeswax; 1 mil contains d-tubocurarine chloride pentahydrate 2 mg. and 48 mg. myricin (wax) in peanut oil.

NICOTINE. (*Not official*).—A colourless, hygroscopic, volatil liquid alkaloid obtained from *Tobacco*.

ACTION AND USES.—The action of nicotine is distributed ove the cerebrum, medulla and cord, the sympathetic and parasympa thetic ganglia, and the motor end-plates of the voluntary muscle These are first stimulated and then depressed, whether it is applie locally, taken internally or given by injection. Nicotine therefor resembles muscarine by stimulating cholinergic nerves and adrena line by stimulating adrenergic nerves, and also acts by liberatin adrenaline from the suprarenal gland.

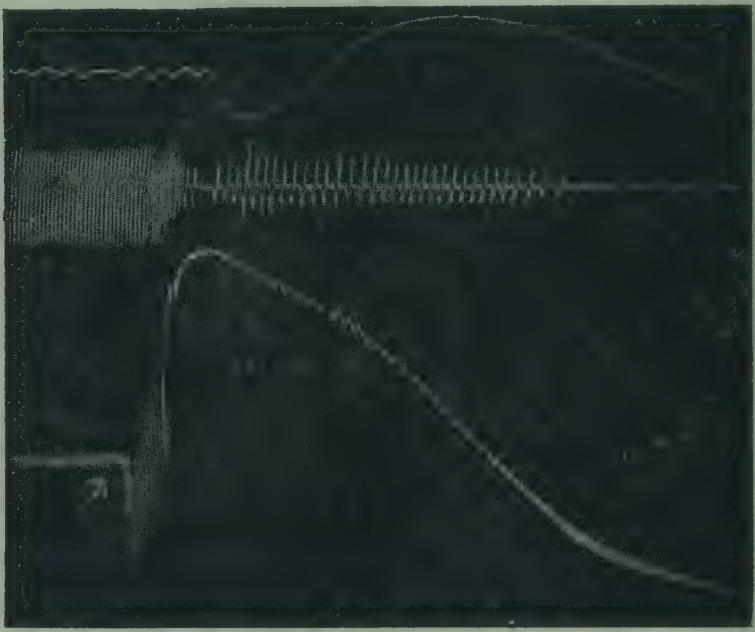


Fig. 14.—Dog. Blood pressure, Respiration and Intestinal Volume

At point of arrow a small injection of nicotine was given. Note slight fa of blood pressure, slowing of the heart from parasympathetic stimulation and i crease of respiration from stimulation of the centre. These are followed by ri of pressure and depression of respiration. Intestinal volume is diminished duri the rise of pressure from constriction of the vessels of the splanchnic area, t vessels are dilated during the fall of pressure.

The heart is first slowed and then accelerated. The initial slov ing is due to stimulation of the vagal centre and excitation of th ganglion cells on the course of the vagus. This is followed by d pression when the sympathetic effect predominates causing acceler tion of the heart. The blood pressure rises enormously from co striction of the vessels, due partly to stimulation of the vaso-mot centre, but also from excitation of the sympathetic ganglion cell particularly those of the solar plexus. This effect is however so followed by fall of pressure. Nicotine therefore causes first slov ing of the heart and rise of blood pressure followed by acceleratic and fall of pressure.

It stimulates the respiratory centre and the breathing becom quicker and deeper. Depression soon follows and death takes pla from respiratory failure. The bronchial muscles are relaxed aft a transient contraction.

It causes through central effect nausea and vomiting. Th

secretions of saliva, sweat and lachrymal glands are increased from stimulation of the ganglion cells on the secretory nerves ; these are diminished after large doses. The smooth muscles are also affected through the ganglia on the nerves supplying them so that these are depressed after a period of stimulation. The stomach and the intestinal tract are powerfully contracted and there may be diarrhoea. These are subsequently paralysed. It first causes contraction followed by paralysis of the voluntary muscles by acting on the neuromuscular junction.

Nicotine is not used in medicine, but its use has been suggested in **post-encephalitic parkinsonism, specially** in those cases where voluntary muscular control is intact but movement is hampered by excessive plastic tone. *Initial dose* is 1/30 gr. (2 mg.) three times daily.

CONII FOLIUM. (*Not Official*). *Syn.*—Hemlock Leaves.—The fresh leaves and young branches of *Conium maculatum*, collected when the fruit begins to form. Contains (1) *Coniine.* (2) *Methylconiine.* (3) *Conhydrine.* (4) *Conic Acid.*

Non-official Preparation

1. **Unguentum Conii.** *Syn.—Hemlock Ointment.*—Extract of conium 7 p.c. in glycerin and simple ointment.

Action and Uses

Applied to the mucous surface it depresses the sensory and motor nerve-endings, particularly the former. The ointment was formerly used to relieve itching of pruritus ani and the pain and spasm of haemorrhoids.

It paralyses the motor nerve-endings similar to curara producing ascending motor paralysis. It also paralyses the sympathetic ganglia after a brief stimulation. The inhibitory ganglia of the vagus in the heart are also paralysed after slight stimulation so that the heart is first slowed and then accelerated. Death takes place from respiratory failure while the heart still beats.

It dilates the pupil, impairs accommodation and causes ptosis from paralysis of the endings of the third nerve.

Gelsemium, B.P.C.—The dried rhizome and root of *Gelsemium nitidum*, the Yellow Jasmine. Contains.—(1) *Gelsemine*, a crystalline alkaloid. (2) *Gelseminine*, mixture of alkaloids, and *Gelsemic* acid ; fats, resins, oils.

Non-official Preparation

1. **Tinctura Gelsemii, B.P.C.**—1 in 10. *Dose.*—5 to 15 ms. or 0.3 to 1 mil.

Action and Uses.—The symptoms of poisoning are more or less the same as observed after conium, *viz.*, diplopia, ptosis, dilatation of the pupil, staggering gait and sleepiness, and finally arrest of respiration.

The heart is depressed in toxic doses with fall of blood pressure from its action on the vagal ganglia. Its effects on the nervous system are the same as observed in conium poisoning except that gelsemine is more depressant. It paralyses the nerve centres first and the endings only after large dose. It causes paralysis of all the muscles of the body by depressing the cells of the anterior cornua of the cord. The motor nerve-endings are affected after large doses.

The tincture is used in neuralgia and **migraine**, specially neuralgia of the fifth nerve. It may be used alone or better with **butylchloral hydrate**.

SPARTEINAE SULPHAS, B.P.C.—A salt of an alkaloid derived from *Scoparii cacumina*, broom tops. In colourless, odourless crystals with a saline bitter taste. *Soluble*, 2 in 1 of water. **Dose.**—1 to 2 grs. or 60 to 130 mg.

Action and Uses

Sparteine resembles coniine in its action but is less poisono It has little effect on the central nervous system. Large doses pa lyse sympathetic ganglia and the motor nerve-endings. The he is slowed and weakened from stimulation of the vagus and at o time it was used in place of digitalis, but in view of the above fa its use as a cardiac stimulant has been given up. It is however le poisonous than conium.

Class F : Drugs Depressing the Sensory Nerve-ending

Local anaesthesia may be produced by various mean Cold applied either in the form of ice, or produced l spraying some volatile substance like ether or ethyl ch ride, will produce anaesthesia in a localised area. Sin this effect lasts only for a few seconds, cold can only l utilised for minor operations, as for instance in openin an abscess cavity or for inserting an exploratory needl etc. Lasting anaesthesia by this method is not possib as prolonged freezing lowers the vitality of the part an produces a tendency to sloughing. Similarly CO_2 snow n only produces anaesthesia by local freezing, but also de troys superficial tissues with which it comes in contac Partial anaesthesia is also produced by rendering the pa anaemic, as by the application of Esmarck's bandage by the use of adrenaline as is often done with cocaine.

Drugs depressing the periphery of the sensory nerv may produce local anaesthesia by lessening the sensibilit of a surface to which they are applied. The most impor ant method of producing local anaesthesia is by the use c certain drugs, specially cocaine and its derivatives. Thes are generally classed as **local anaesthetics.** An ide anaesthetic should produce paralysis of the sensory nerv or nerve-endings only temporarily, and in concentratio much lower than which will cause destruction of tissues.

With the introduction of many different preparation and with the advance of our knowledge, local anaestheti are now extensively used for many operations which we formerly performed under general anaesthetics. In fa certain operations are now performed under local anae thetics in preference to chloroform and ether.

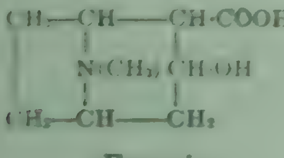
There are however other drugs which possess feeb local anaesthetic action, and are used generally when pa is present, and are known as **local anodynes.** These a used for application to the unbroken skin, and act eith by directly paralysing the nerve-endings, or by centr effect. Some of them are used for local sedative action o the stomach, to relieve vomiting or gastric irritation.

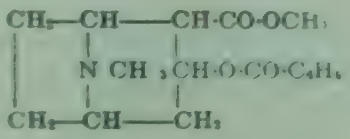
Local anodynes are.—Menthol, chlorbutol, camphor, belladonn hydrocyanic acid dilute, chloroform, opium, aconite, phenol, ur quinine.

COCAINA

Cocaine. (Cocain.). $C_{17}H_{21}NO_4$

Source.—It is *methylbenzoylecgonine*, an alkaloid obtained from the leaves of *Erythroxylum Coca*, and other species of *Erythroxylum*, or by synthesis from ecgonine.


Ecgonine


Cocaine

Characters.—Colourless crystals; odourless, with a bitter taste followed by a sensation of tingling and numbness. Almost *insoluble* in water, soluble in 10 parts of alcohol (90 p.c.), in 4 parts of solvent ether, 24 parts of olive oil and in 120 parts of liquid paraffin.

COCAINAE HYDROCHLORIDUM. (Cocain. Hydrochlor.).—Cocaine Hydrochloride is the hydrochloride of the alkaloid cocaine.

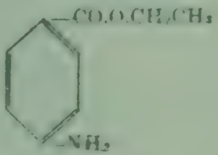
Characters.—In colourless, transparent crystals; odourless; taste, bitter followed by a sensation of tingling and numbness. *Solubility.*—In 0.5 part of water, 1 in 3 of alcohol (90 p. c.), insoluble in olive oil.

B. P. Dose.—1/8 to 1/4 gr. or 8 to 16 mg.

Official Preparations

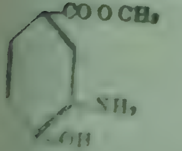
1. **Oculentum Cocainae.**—Cocaine hydrochloride 0.25 p. c.
2. **Lamellae Cocainae.**—1/50 gr. (1.3 mg.) in each.
3. **Trochisci Krameriae et Cocainae.**—1/20 gr. or 3 mg. of cocaine hydrochlor. in each.
4. **Suppositoria Cocainae.**—Contains 1/4 gr. each.

Benzocaina. (Benzocain.). Syn.—Anaesthesine; Ethyl Aminobenzoate.—Benzocaine may be prepared by the reduction of ethyl *p*-nitrobenzoate.



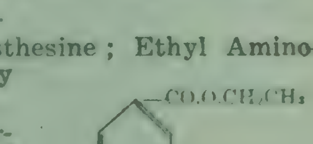
Characters.—A white crystalline powder; odourless; taste, slightly bitter, followed by a sensation of numbness. *Soluble* in 2500 parts of water, in 8 parts of alcohol (90 p. c.).

Orthocaina. (Orthocain.). Syn.—Orthoform.—Orthocaine is the methyl ester of *m*-amino-*p*-hydroxybenzoic acid prepared by esterifying with methyl alcohol the reduction product of 3-nitro-4-hydroxybenzoic acid.



Characters.—A white, or faintly yellow, crystalline powder; no odour or taste. Sparingly *soluble* in water; soluble in 7 parts of alcohol (90 p. c.), in 50 parts of solvent ether, readily in solution of caustic soda.

Procainae Hydrochloridum. (Procain. Hydrochlor.). Syn.—Ethocaine Hydrochloride; "Novocaine:" "Kerocaine."—Procaine Hydrochloride is prepared by the interaction of chloroethyl-diethylamine and sodium *p*-aminobenzoate.



Characters.—Colourless, crystalline, powder; odourless; taste, weakly bitter, followed by a transient numbness of the tongue. Stable in air. Soluble in 1 part of water, and in 8 parts of alcohol (90 p.c.).

Official Preparations

1. Injectio Procainae et Adrenalinae Fortis.—Procaine hydrochloride 2 p.c. w/v and solution of adrenaline hydrochloride 2 p.c. v/v.
2. **Injectio Procainae et Adrenalinae Mitis.**—Solution of procain. hydrochlor. 2 p.c. [illegible]; inj. sod. chlor. 750; inj. adrenalin. 2.

Amethocainae Hydrochloridum. (Amethocain. Hydrochlor.)

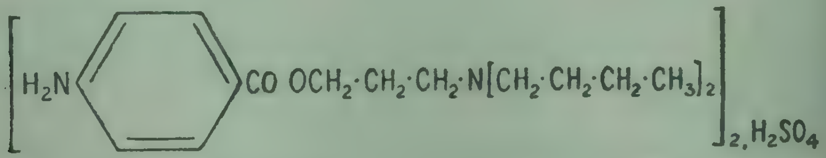
Syn.—Tetracaine Hydrochloride ; Decicaine ; Pontocaine.—Ametho caine Hydrochloride is the hydrochloride of the *p*-*n*-butylaminobenzoi ester of β-dimethylaminoethanol.

Characters.—A white, crystalline powder : odourless ; taste, slightly bitte followed by sensation of numbness. Very *soluble* in water ; soluble in alcoh (95 p. c.) ; insoluble in solvent ether, in benzene.

Official Preparation

1. **Injectio Amethocainae Hydrochloridi.** *Syn.—Injection of Tetracaine Hydro chloride.*—Contains 88.5 to 111.0 p.c.

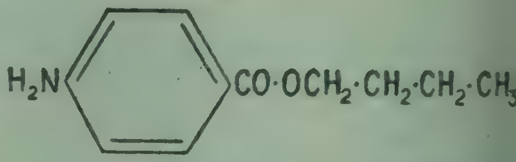
Butacainae Sulphas. (Butacain. Sulph.). **Syn.**—Butyn.—Buta caine Sulphate is sulphate of the base of γ-di-*n*-butylaminopropyl-*p* aminobenzoate.



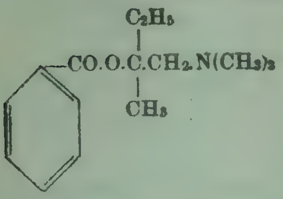
Characters.—A white, crystalline, odourless powder. Taste, slightly bitte followed by transient insensibility of the tongue. *Soluble* in less than 1 part water, more rapidly on warming ; less than 1 part of warm alcohol (95 p.c.).

Butylis Aminobenzoas. (Butyl. Aminobenz.). **Syn.**—Butesin.— Butyl Aminobenzoate is *n*-butyl-*p*-aminobenzoate.

Characters.—A white, crystalline, colourless powder ; tasteless. Very slightly *soluble* in water ; soluble in dilute acids, in alcohol (95 p.c.), in chloroform, in solvent ether, and in fatty oils.



Amylocainae Hydrochloridum. (Not official). **Syn.**—Stovain



Characters.—Colourless, crystalline powder ; tast bitter, followed by a transient insensibility of t tongue. *Soluble* in 2 parts of water, and in 3 parts dehydrated alcohol.

Dose.—By mouth and subcutaneously.—1/3 3/4 gr. or 20 to 50 mg. By intrathecal injection.— 1/3 to 1½ grs. or 20 to 100 mg.

Non-official Preparations and Derivatives

1. **Tropacocaine.** *Syn.—Benzoyl-pseudo-tropine.*—Obtained from Java coc Is alleged to be safer, more rapid, and less irritating to the eye, without dilati the pupil. Its **hydrochloride** is freely soluble in water. Very costly. Used in p. c. solution.

2. **Alypin.** *Syn.— Amydricaine Hydrochloride ; Benzoyl tetramethyl-diamin ethyl-dimethyl-carbinol hydrochloride.*—A white crystalline powder. Readily solul in water, giving solution of a neutral reaction. A *local anaesthetic*, used hypode mically for minor operations and in ophthalmic practice. It is equal in intensi and toxicity to cocaine. May be used in strengths of from 1 to 4 p. c. *Dose.* **1/20 to 1/2 gr. or 3 to 30 mg.**

3. **Borocaine.** *Syn.—Ethocaine Borate.*—A white crystalline powder. Neith toxic nor irritant. Being a salt of weak acid, in solution yields free alkaloidal ba by hydrolysis. *Dose.*—**1/3 to 1½ grs. or 20 to 100 mg.**

4. **Benzamine Lactate, B.P.C.** *Syn.—Eucainae Lactas.*—A white crystalli powder soluble in 5 parts of water and in 8 parts of alcohol (90 p.c.). *Dose.* **1/8 to 1/2 gr. or 8 to 30 mg.**

5. **Spinocain.**—Contains novocaine 0.2 grm., strychnine sulph. 2.2 mg. ; 14.5 p.c. alcohol in normal saline 2 mils. Also contains Gliadin which preven diffusion in the subarachnoid space until the anaesthetic has been absorbed.

Pharmacology

Cocaine is a general protoplasmic poison and caus irritation and destruction of cells. It stops movements

leucocytes, amoebae and ciliated cells. A 5 p. c. solution given subcutaneously may cause death of the tissues, producing either necrosis or a sterile abscess. For the same reason its application to the eye may result in cloudiness or ulceration of the cornea, but this is not ordinarily observed.

Locally.—Cocaine has no action on the unbroken skin, although a 10 p.c. ointment may produce a demonstrable depression of sensation, but no true local anaesthesia (Clark). Applied to the mucous membrane or injected subcutaneously it causes blanching by constricting the local blood vessels and stimulation of the vaso-constrictor nerve-endings, and **anaesthesia** from the paralysis of the sensory nerves. Since these effects are local it follows that the drug must be applied in sufficient concentration to reach the nerve supply of the part which it is desired to influence. Although the sense of pain is abolished, the sense of touch is not so readily lost, and the temperature sense is scarcely affected, if at all. If the solution is made alkaline by the addition of sodium bicarbonate its efficacy is increased 2 or 4 times, due to easier penetration of the free anaesthetic base as compared with its salts, specially when injected into nerve trunks, and probably for subdural injection and on application to mucous surfaces (Sollmann). These effects may be produced by a 5 to 10 p. c. solution in about one to four minutes, and will last from fifteen minutes to an hour. The period however depends upon the concentration of the solution used and the vascularity of the part. Its action is prolonged and intensified by the addition of adrenaline, which still further constricts the vessels and prevents its rapid removal by the circulation.

Injected along the trunk of a mixed nerve it paralyses the sensory fibres and abolishes pain of the area supplied by that nerve but the motor impulses pass through the nerve unimpaired. This method of producing anaesthesia is known as "nerve blocking" or "regional anaesthesia." Injected intrathecally by lumbar puncture it abolishes sensation below the umbilicus though the power of movement remains unimpaired. This method of anaesthesia is adopted for the production of "intraspinal anaesthesia."

It should be noted that anaesthesia is produced only on local application and when taken internally it causes partial loss of sensation only in those parts with which it comes in contact, namely, mouth, throat, oesophagus and stomach and no anaesthesia is produced after absorption. This is because the drug paralyses the central nervous system in much lower doses than those necessary to paralyse sensory nerve-endings after absorption.

Internally. **Gastro-intestinal tract.**—Locally applied

cocaine abolishes sensation of taste of the tongue, palat and fauces. The same anaesthetic effect is noticed in th stomach and cocaine diminishes gastric secretion an deadens the sensation of hunger, although the appetit appears on the sight of food. In experimental works wit strips of intestine, cocaine augments their movements This effect is due to the direct action of the drug on th muscles. In large doses it checks peristalsis.

Heart and circulation.—After a momentary slowin the heart beats faster. This effect was at one tim thought to be due to paralysis of the vagus, but since th stimulation of the vagus slows the heart even in lat poisoning, the acceleration must be due either to its direc action on the muscle or stimulation of the accelerato mechanism. After large doses the heart becomes weal and slow either from direct muscular depression or vagu stimulation, and death may take place from cardiac failure In the earlier stages of poisoning the **blood pressure rise** considerably from stimulation of the vaso-constricto centre together with the increased rate of the heart. Th pressure subsequently falls. As already noted cocain causes constriction of vessels when locally applied, but n such effect is observed in general poisoning as it does no circulate in sufficient concentration to produce the effec as that would be fatal to the heart and respiration.

Respiratory tract.—Topically applied it deadens th sensibility of the nasal mucous membrane. Given inter nally it first increases the respiratory movements from stimulation of the respiratory centre but soon depresse them. During the spasms respiration becomes irregula and assumes a Cheyne-Stokes type. Death results from asphyxia due to respiratory failure.

Nervous system. *Cerebrum.*—Cocaine **stimulates** th entire central nervous system, and in small doses it in creases the higher functions of the brain, while in ma there is some psychic stimulation and wakefulness (caffein action). In large doses it acts like atropine producin talkativeness and cheerfulness, and a feeling of comfor and ease with the abolition of mental and bodily fatigue For these effects coca leaves are largely used by the peopl of Peru and Bolivia. All observers agree that it increase muscular work and possibly like caffeine increases menta powers when taken in small quantities. Often it cause sleeplessness though without much discomfort.

The **respiratory**, **vaso-motor** and **accelerator centre** and the motor areas of the brain are **stimulated**, and ther is a tendency to motor activity and restlessness. These effects are central, and therefore are antagonistic to opium Larger doses induce convulsions, which are not of spina origin, but produced by some action on some undetermine

part of the hind-brain. At an earlier stage the medulla is affected when the respiration is quickened with evidence of reflex excitability which in toxic doses may become so exaggerated as to cause convulsions like strychnine. Cocaine first stimulates the brain, then the mid-brain and finally the cord, the action being one of descending stimulation. In other words with small doses the symptoms arise from the brain, but as the dose is increased those from the lower part of the nervous system become manifest. This stimulation is followed by depression, first affecting the cerebrum, then the bulb and lastly the cord.

Cocaine **potentiates** the effect of adrenaline. It also potentiates both the excitatory and inhibitory responses of muscles and glands to adrenaline or adrenergic nerve impulses. It possibly enhances the production of sympathin or prevents the destruction of adrenaline or sympathin by neutralising amine oxidase ; or may increase the permeability of sympathetically innervated cells and thus favours the stimulating agent.

Eye.—A 4 p.c. solution dropped into the eye causes complete **anaesthesia** of the conjunctiva and cornea, and partial anaesthesia of the iris, **dilatation of the pupil,** exophthalmos and vaso-constriction. It partially **impairs** the range of accommodation but the light reflex is not lost. The dilatation is not maximum, since atropine causes a further dilatation when applied to a cocainised eye. These effects have been attributed to the stimulation of the sympathetic nerve-endings, and as they are more quickly produced when the drug is applied topically than when taken by the mouth, they appear to be due to direct local action. On the other hand some hold that dilatation is caused by the weakening of the circular fibres of the iris, much in the same way as other unstriped muscles are affected. The oculo-motor endings are not affected unless strong solutions are used when there is some impairment of accommodation. It slightly lowers the intra-ocular tension due to vaso-constriction, but this effect is not constant.

Metabolism is not much altered. The temperature rises in cocaine poisoning, due essentially to increased heat production from muscular excitement.

Elimination.—It is eliminated in the urine, the quantity of which is increased *pari passu* with dilatation of the vessels of the kidneys, although at first they are contracted when the secretion is diminished. A portion is excreted *via* the liver while a small quantity is retained in the tissues and eliminated slowly so that cocaine may be cumulative after repeated doses. It is also destroyed in the liver.

Acute toxic action.—Acute poisoning is not infrequent. Susceptibility varies due partly to uncertainty of absorption and partly to rapid destruction and idiosyncrasy. Ordinary fatal dose is 18 grs.

though death may take place from 1/8 gr. Toxic symptoms hav been produced from a hypodermic injection of 1/4 gr. Wakin hallucination like those in poisoning by Indian hemp, leading some times to mania, vertigo, occasionally dryness of the throat, respira tory and cardiac difficulty, cramps in the limbs, inability to move and a sensation of foreign bodies, such as pebbles or worms, especi ally the latter moving under the skin, are characteristic. Pupil dilate and reflexes are exaggerated. After very large doses epilepti form convulsions accompanied by circulatory and respirator depression occur. Death takes place through failure of respirator centre or collapse with very low blood pressure.

Treatment.—As a preventive during local anaesthesia previou use of sedatives like barbiturates half an hour before by the mout diminishes risk. Adrenaline or ephedrine hypodermically in spina anaesthesia. In *poisoning*, luminal sodium or amytal sodium, paral dehyde or inhalation of ether or chloroform to check convulsion For collapse, adrenaline 0.5 mil (8 ms.) with saline. Artificia respiration.

Chronic toxic action or "Cocainism."—Like coca craving, cocain omania is developed either in shaking off morphine or alcoho habit or from the temporary use of cocaine as a stimulant. Cocain habit is rapidly increasing notwithstanding law against the sale o this drug. It is more dangerous to the health and moral than opium, and its habit increases sexual desire in both men and women and also causes perverted sexual passion. It is taken with prepared *pan* in India, but as a snuff in other countries, which causes irrita tion of the nasal mucous membrane with perforation of the nasa septum. Disordered digestion, emaciation, giddiness, quick pulse insomnia, dilated pupil, visual or other hullucination, amnesia and impotence are prominent symptoms. Habitues may consume up to 10 or sometimes 20 to 30 grs. Total abstinence from the drug strong coffee, nux-vomica, and other tonics, change of air, etc. remove this pernicious habit.

THERAPEUTICS

Externally.—Cocaine is chiefly used as a *local anaes-thetic* :—

Eye.—Cocaine is largely used in ophthalmic practice as an anaesthetic during operation, for relief of pain, and as an astringent to constrict the vessels of the iris in inflammatory conditions. A 1 to 2 p.c. solution will allay pain while a 4 p.c. solution or the official lamel dropped on the conjunctiva every three minutes 3 to 5 times, so far removes the sensibility as to enable the surgeon to perform many operations, as for example, cataract, etc., painlessly. Photophobia, conjunctival and corneal pain are soon relieved by the same collyrium. Combined with atropine sulphate, cocaine has been found very efficacious in iritis and in many painful inflammatory affections of the cornea. By adding ½ gr. of pilocarpine nitrate to 1 dr. of a 4 p.c. solution, we can anaesthetise the eye without affecting the accommodation.

Nose, ear, anus, vagina, etc.—A 5 to 10 p.c. solution removes the sensibility of the mucous membrane of the nose, internal meatus of the ear, vagina, urethra and rectum, so as to allow small operations to be performed painlessly. The

nasal irritation in hay fever, anal and labial pruritus, earache, and the pain of anal fissure or ulcer are all relieved by the local application of cocaine.

Skin.—Although cocaine is known not to be absorbed by the intact skin, yet the application of the alkaloid combined with lard or oil allays the burning and pain of eczema, erysipelas, urticaria, sore nipples, etc. The pain and irritation of **burns** and **scalds** are soon relieved, if the part is first brushed over with a 4 p.c. aqueous solution of cocaine hydrochloride and then the pure alkaloid combined either with carron oil or with paraffin or boric acid ointment is applied. A hypodermic injection of cocaine or novocaine removes the pain of scorpion-stings.

Internally. **Gums and teeth.**—Cocaine, preferably the alkaloid, as it is less likely to be washed away by the saliva, is largely employed in dentistry to deaden the sensibility of the exposed pulp. Cocaine hydrochloride 1, chloral hydrate 5, and camphor 5, form an oily liquid when warmed which removes toothache. A tooth may be painlessly extracted by injecting a solution into the gums at its base, but this is a risky procedure. The mere rubbing of cocaine over the gums deadens their sensibility to such an extent as to annul the pain of the first application of the forceps.

Throat and larynx.—By applying a 20 p.c. solution to the soft palate and pharynx, enlarged tonsils or small growths, these may be excised, or the galvano-cautery applied, painlessly. By the same method the larynx may be explored and minor operations performed there without spasm or pain. In painful sore-throat cocaine and rhatany lozenges give great relief by acting locally.

Stomach.—For its local effects on the gastric mucous membrane, it may sometimes be used in **sea-sickness** and **vomiting of pregnancy.** $\frac{1}{8}$ gr. with 15 ms. of glycerin in 60 ms. of water may be given every hour for this purpose.

Uses of Local Anaesthetics in Major Operations

Intraspinal anaesthesia.—By the direct application to the spinal cord of local anaesthetic drugs the passage of both afferent and efferent impulses along the spinal roots may be blocked. The drugs commonly used for the purpose are stovaine (amylocaine hydrochloride), novocaine (procaine hydrochloride) and cinchocaine. Cocaine is not used as being too dangerous, and procaine and cinchocaine have almost replaced stovaine. Stovaine is used in two forms: One contains 0.1 grm. each of stovaine and glucose in 2 mil. and with sp. gr. 1.025. The other (Chaput's formula) is a 10 p.c. solution with sp. gr. of 1.086, and the dose is 0.2 to 0.5 mil. Some cases of permanent incontinence followed its use.

A form of spinal analgesia extensively used in the Continent and America is by injecting the anaesthetic into the small layer of the loose tissue outside the dura. This method is allied to sacral analgesia.

But all these drugs have the drawback of being effective only in fairly concentrated solution and spreading towards the head by gravitational diffusion when a Trendelenburg position is adopted during operation necessary to maintain blood pressure. The intro-

duction of nupercaine has altered the position. Although high toxic it can be used in very high dilutions.

Spinal anaesthesia should be confined to operations below t nipple line, though claims have been made that anaesthesia can induced as high up as the head, and such operations as enucleati of the tonsils have been performed. But unless undertaken by ve expert hands this may lead to dangerous paralysis of the respirato centre with fatal result. It is an ideal method for gynaecologic operations, and for operations upon the rectum and bladder, and diabetics. It is specially useful for persons who have a dread f chloroform or ether, or for losing consciousness. Since it blocks t nervous paths of shock impulses, it is an ideal anaesthetic for cas where shock from operation is anticipated, but should be avoid where the nervous shock is already present.

A frequent complication is retching and vomiting which mak abdominal operation rather disturbing. Failure of respiration som times gives rise to grave anxiety. This effect is supposed to indirect through insufficient blood supply from excessive fall blood pressure. The condition should be treated with oxygen, oxygen and 5 p.c. carbon dioxide. Some fall of blood pressure always present and this is not of any consequence.

Injection into the nerve sheath (intraneural) is used when permanent effect is desired as into the cut nerves in amputatic stumps.

Anesthesia by the local infiltration method consists in subc taneous injection of either 0.1 p.c. of cocaine, or 0.24 p.c. of eucair with 0.8 p.c. of sodium chloride, along the proposed lines of incisio and then into the deeper parts before cutting them. Noway cocaine is rarely used for the purpose, as it produces toxic symptom and procaine is widely used, which in suitable doses is free fro any toxicity; moreover, the solution can be sterilised by boilin As it does not constrict the arterioles, a little adrenaline chlori solution (0.002 to 0.005 p.c.) is added to check haemorrhage, to pro long the period of anaesthesia and to reduce toxicity. The strengt of the solution is 0.25 to 1 p.c. and the usual procedure is to sta by raising on the skin over the required area a number of wheal by injecting the solution endermically. After a number of thes wheals have been formed insert the needle deep into the tissues. I this way quite a large area can be made anaesthetic, and if neces sary can be extended to deeper tissues by subsequent injections.

Regional anaesthesia.—In this the anaesthetic is used to bloc the passage of pain impulses by exposing the sensory nerve trunk to the anaesthetic solution leaving the nerve-endings unchanged, s that sensation of pain does not reach the central nervous syste After a preliminary local anaesthesia the drug is injected into th nerve trunk or around it to cause a temporary sensory and moto paralysis. Procaine is the drug of choice and a 2 p.c. solution used. In the infiltration anaesthesia, the actual nerve-endings o the part to be operated upon are anaesthetised.

Regional anaesthesia has been largely used, and with much suc cess, in gastric surgery by blocking the greater and lesser splanchni nerves by infiltrating the loose retro-peritoneal tissue around th coeliac plexus with a 5 p.c. solution of procaine and adrenalin By this method, the stomach, small intestine, omentum, liver an hilus of the spleen can be sufficiently anaesthetised to be handle painlessly. The abdominal wall and parietal peritoneum are pre viously anaesthetised by the local infiltration method.

Local anaesthetics and sulphonamides.—Since sulphonamides ar inhibited by *p*-aminobenzoic acid, analgesics which contain this com plex should not be used in infiltration anaesthesia when sulphona mide derivatives are applied to wounds.

Those containing the *p*-aminobenzoic acid group are: Benzo

caine, Orthocaine, Procaine, Amethocaine, Butacaine and Butyl aminobenzoate.

Toxic effects of local anaesthetics.—Quite a large number of operations are now performed with the aid of local anaesthetics, and since this entails the use of these drugs in large doses their toxic effects should be carefully noted. It should be remembered that local anaesthetics are protoplasmic poisons possessing special affinity for nerve tissue, injections of large amounts in solution will naturally affect the brain and the vital centres. The symptoms of overdosage are excitement, restlessness, deep and rapid breathing, dilated pupil, and feeble pulse. These are followed in severe cases by unconsciousness, convulsions and death. According to Farr intravenous lethal dose of a local anaesthetic is one-tenth of its subcutaneous lethal dose. Accidental introduction into a vein therefore is responsible for most of the cases of sudden collapse and death. Adrenaline increases the liability to cardiac failure by causing fibrillation of the ventricle as happens after chloroform anaesthesia.

Procaine is considered to be the safest. Given subcutaneously the total quantity should not exceed 0.2 grm. (3 grs.) when used in 2 p.c. solution. It is better not to exceed a concentration of more than 1 p.c. It injures the kidney and may cause albuminuria.

After-effects.—Apart from the after-effects seen after general anaesthesia, severe headache is a common trouble and has been attributed to increased intracranial pressure. It is occipital or suboccipital and may be aggravated by raising the head. Some temporary relief is obtained by lumbar puncture. Mild cases yield to ordinary treatment. In severe forms, hypertonic saline infusion or an intravenous injection of glucose and saline (50 p.c. glucose), or 2 mils of 50 p.c. magnesium sulphate are useful.

Transient paralysis of the sphincters of the bladder, or squint may appear, which disappears within a few weeks.

The following are the disadvantages of using cocaine :—

1. **Its general poisonous action.**
2. **Growth of fungus on keeping.**
3. Its tendency to formation of vicious habit.
4. **It is destroyed by boiling.**

Contra-indications.—The chief contra-indication to the injection of local anaesthetics is the presence of sepsis. As full consciousness is retained during the operation, it is unsuitable for children and highly nervous adults. They are best treated under general anaesthetics. In debilitated patients the vitality of the tissues may be unable to withstand the increased pressure of the injection and sloughing may result.

Different Local Anaesthetics

Benzocaine was introduced under the name of *Anaesthesine.* It is insoluble in water but fairly soluble in oil, and is largely used as a surface anaesthetic in the form of dusting powder mixed with starch or talc powder in the proportion of 10 to 15 p.c., in burns, ulcers, eczema, etc. It may also be used as an ointment (10 p.c.). As a suppository (10 grs.) it may be used in painful and inflamed piles.

Procaine hydrochloride or *Novocaine* has a wide field of usefulness and has replaced cocaine in injection anaesthesia as it is less toxic and less irritating, but the effects are less prolonged. Since it is absorbed with difficulty from mucous surfaces it cannot reduce pain when applied to the conjunctiva, nose, or urethra. It does not constrict the vessels, rather dilates them, and therefore it is usually combined with adrenaline which makes it less toxic by diminishing absorption and prolongs its effects. The usual strength for injection is 0.5 to 2.0 p.c. The solution can be sterilised by boiling. For the production of regional or infiltration anaesthesia it is largely used in

place of cocaine. For extensive infiltration 300 mils of a 0.5 p. solution may safely be used ; for nerve block 40 mils of a 2 p. solution are recommended but in actual practice such large quant ties are not required.

Intravenous Procaine

Intravenous administration of procaine hydrochloride has bee introduced for the treatment of many clinical conditions, namely, (a as an **analgesic** for the relief of pain in burns and arthritis, as a sub stitute for morphine in post-operative care, and also for relief c traumatic and inflammatory pains ; (b) as a **vasodilator** in vascula diseases like thromboangiitis obliterans, coronary insufficiency ; (c to **reduce cardiac** arrhythmias associated with cyclopropane anaes thesia both as a prophylactic as well as a rapidly effective thera peutic measure.

Procaine is hydrolysed in the plasma into p-aminobenzoic aci and diethylaminoethanol the latter possessing a tri-alkylamin group also present in a number of compounds like Benadryl, Peth dine, Quinidine, etc., which have some properties in common, i.e they are local anaesthetics, spasmolytics, analgesics and ant allergics. Procaine is, therefore, used in certain allergic states lik urticaria, serum sickness, penicillin-sensitivity reaction and asthma

Administration and Dosage.—The safety of intravenous pro caine administration depends on the rate of destruction by procain esterase in the blood and liver.

A 0.1 per cent. procaine hydrochlor. in saline in dosage of 4 mg. kg. body weight is administered slowly taking over 20 minutes ; no more than 10 mils. (100 mg. of procaine) should be given at a time **Symptoms immediately** following the injection are feeling of warmt throughout the body, flushing of the head and neck, dryness of th mouth, mydriasis, light-headaches and a feeling of relaxation. Wit rapid infusion there may be even convulsion which is counteracte by barbiturates and it is suggested that as a preventive measur barbiturate should be used prior to the intravenous administratio of procaine.

Amylocaine hydrochloride or *Stovaine* is slightly less toxic tha cocaine and is preferred for intraspinal anaesthesia. It is howeve slightly more toxic than procaine. It is an irritant and cause hyperaemia, does not constrict vessels nor cause dilatation of th pupils. If the solution comes in contact with the medulla it ma cause profound fall of blood pressure and stoppage of respiration.

Orthocaine is largely used as a local anaesthetic to abraded an mucous surfaces and is used for its local effect to relieve gastric pai in ulcers, simple or malignant, in 1 to 2 gr. doses, and as a dustin powder or as an ointment (10 p.c. in simple ointment) to relieve pai in burns, ulcers, etc. It has the drawback of producing severe irrita tion and even necrosis.

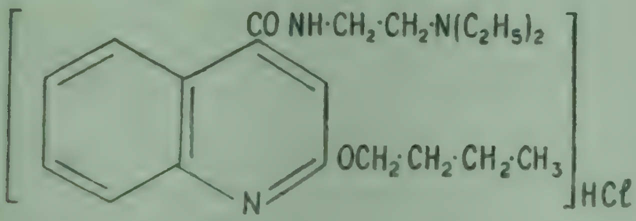
Amethocaine or *Pontocaine* is fifteen times as active as procain and ten times as active as cocaine, but is more toxic. A 0.5 p.c solution is used in ophthalmic practice, but may cause irritation o turbidity of the cornea. A 2 p.c. solution is used for surface anaes thesia and 0.1 p. c. solution in normal saline with adrenaline is use for regional anaesthesia ; and 0.5 to 1 p. c. solution for spina anaesthesia.

Lignocaine or *Xylocaine.*—It is Diethylaminoact-*m*-2-xylide. local anaesthetic less toxic than other local anaesthetics Used i the same concentration as procaine and has a more prolonged effect It is stable on boiling and more resistant to the action of acids an alkalies. It has a good surface action when used in strengths o 2 to 4 p.c.

In the following table the differences in the action of cocaine, nupercaine and procaine have been summarised.

	Cocaine	Cinchocaine or Nupercaine	Procaine or Novocaine
Toxicity	High	8 times of cocaine but used in very dilute solution	Low ; 1/5 th to 1/7 th of cocaine
Irritation and tissue injury	Non-irritant in ordinary concentration	Little. For conjunctiva use with caution	Non-irritant
Vaso-constriction	Yes	Nil	Dilates vessels
With adrenaline	Prolongs effect	More efficient	Vaso-constriction. Acts efficiently
Stability of solution	Slowly deteriorates. Should be freshly made	Keeps well but destroyed by trace of alkali	Keeps well but gets discoloured
Sterilisation	Destroyed by boiling. Can be brought to boiling point	Decomposed by boiling	Can be boiled
Pupil	Dilates	Nil	Nil
Surface anaesthesia	Efficient	Very efficient	Not efficient
Uses	Useful for surface anaesthesia with adrenaline	Very useful for surface and spinal anaesthesia ; also for infiltration anaesthesia	Useless for surface anaesthesia Useful for spinal and infiltration anaesthesia

Cinchocainae Hydrochloridum. Syn.—Nupercaine ; Percaine.—Cinchocaine Hydrochloride is the hydrochloride of the β-diethylaminoethylamide of 2-butyloxycinchoninic acid.



Characters.—Fine, white, hygroscopic crystals ; odourless ; taste, slightly bitter. *Soluble* in 0.5 part of water, freely in alcohol (95 p. c.).

Action and Uses

Nupercaine has been used for its local anaesthetic effect in the form of an ointment (1 p. c.) in pruritus, chilblains, piles, etc., and as lozenges in sore throat, aphthae and to relieve post-tonsillectomy distress.

Nupercaine differs from the above group in being a derivative of quinoline, a group of substances not used as local anaesthetic. It is soon decomposed by the presence of a trace of alkali, and must be kept in alkali-free glass containers, and syringes, needles, etc., must be boiled in water free from any alkali and should not come in contact with tap water or Ringer's solution. The drug was introduced by Karl Meischer and since then it has profoundly modified the technique of spinal analgesia. It is a much more powerful local anaesthetic than either cocaine or procaine and is about twenty-five times more toxic than procaine and three times than cocaine but this is offset by the fact that its minimal effective concentration is about one-fortieth. It is also extremely effective for surface application, and has a more prolonged action than cocaine. A dilution of 1 in 125,000 has a demonstrable effect on rabbit's cornea, whereas

it requires 1 in 10,000 to produce the same effect with cocaine. A
though it is largely used for spinal anaesthesia symptoms of poiso
ing were observed after excessive doses, viz., clonic convulsic
irregularity of the heart, circulatory failure, cyanosis and respirato
paralysis.

For *local anaesthesia* to mucous surface a 1 to 2 p.c. soluti
with a few drops of 1 in 1000 adrenaline is sufficient. For *infiltr
tion anaesthesia* the strength is 0.5 to 1 in 1000, with the addition
10 to 20 drops of 1 in 1000 adrenaline solution for every 100 mils
anaesthetic. For *spinal anaesthesia* a 1 in 1500 solution in 0.5 p
saline is used, and of this 6 to 18 mils are required. As the sol
tion is lighter than the cerebrospinal fluid the patient should lie
his face with his buttocks slightly raised for at least five minute
This enables the solution to reach the posterior nerve roots. An i
jection of ephedrine or adrenaline is given at the same time
combat any fall of blood pressure.

Sterile solutions of 20 mils ampoules of 1 in 1500 in 0.5 p.
saline are available.

It has the following advantages over procaine :—

1. It is a powerful anaesthetic to mucous surfaces.
2. When given by injection the effects last for several hour
while with procaine they last only for half to one hour.
3. The minimum effective concentration is so small that for a
practical purposes it has no toxicity.
4. There is less fall of blood pressure and therefore less shock

GROUP VI
DRUGS ACTING ON THE MUSCLES

The muscles of the body are voluntary or skelet
(striated), involuntary (non-striated) and cardiac.

The voluntary muscles are under the control of wi
and a special mechanism exists for their function. Th
when one group of muscles, *e. g.* the extensors, contrac
opposite group, *viz.*, the flexors, relax ; thus facilitatin
movements (law of reciprocal innervation).

All motor nerves whether supplying the voluntary
involuntary muscles act by liberating at their ends chemic
substances which carry impulses across the synapse an
act upon the muscle cells. These nerves can be broadl
classified into two groups according to the nature of th
substances liberated, viz., *cholinergic* and *adrenergic*. Th
acetylcholine liberated at the motor nerve-endings is re
ponsible for transmitting the nerve impulse to muscle fibre
and for initiating muscular contraction, and the enzym
choline esterase, which is found to be specially concentrate
near the motor end-plates, causes inactivation of the tran
mitter, just as is observed in the autonomic nervous system
The sympathetic is supposed to antagonise the onset
fatigue in the voluntary muscles in an unknown way, a
though adrenaline, the sympathetic transmitter, increase
the excitability and contractility even in an unfatigue
muscle, and ephedrine, another sympathomimetic dru
possesses an anti-curari action.

The motor nerves to the voluntary muscles originate

the anterior horn cells of the spinal cord and the corresponding group of cells in the motor cranial nuclei ; these constitute the *lower motor neurone.* The anterior horn cells again receive impulses from and are controlled by the precentral gyrus of the cerebral cortex, through the motor fibres arising from it, constituting the *upper motor neurone.* It will be seen that there is no direct anatomical continuity between these two neurones, but the nerve impulse passes from one to the other by contact. The lower motor neurone is also under the control of the extra-pyramidal system.

The motor area is largely influenced by the psychic area of the brain, stimulation of which results in diminished sense of fatigue and increased muscular power.

CLASS A : **Drugs which act on the voluntary muscles**

I. Drugs which stimulate the voluntary muscles

(*a*) *Those acting on the psychic area of the brain* : Caffeine, Cocaine.

(*b*) *Those acting on the motor area of the brain* : Atropine.

(*c*) *Those acting by stimulating the cord*: Strychnine, Brucine and Thebaine.

(*d*) *Those acting by stimulating the motor nerve-endings* : Cholinergic drugs (Acetylcholine, Carbachol, Physostigmine, Neostigmine), Potassium, Ephedrine and Guanidine. All these possess anticurari action.

(*e*) *Those acting directly on the muscle* : Veratrine, Caffeine, Potassium.

II. Drugs which depress the voluntary muscles

(*a*) *Those acting by depressing the motor area of the brain* : Hypnotics, Hydantoins, Narcotics and General Anaesthetics and Magnesium.

(*b*) *Those acting by depressing the cord* : Bromides, Chloral Hydrate, Mephenesin.

(*c*) *Those acting by depressing the motor end-plates* : Curare, Conium, Magnesium, certain Snake Venoms.

(*d*) *Those acting by depressing the muscle directly* : Quinine.

CLASS B : **Drugs which act on the involuntary muscles**

The nervous mechanism controlling the involuntary muscles has already been discussed (*see* page 229).

I. Drugs which stimulate the involuntary muscles

(*a*) *Those acting by stimulating the parasympathetic nerve-endings* : Cholinergic drugs ; these stimulate the plain muscle of the intestine, bronchi, urinary bladder, the splenic capsule and the circular fibres of the iris.

(*b*) *Those acting by stimulating the sympathetic nerve-endings* : The sympathomimetic drugs : Adrenaline, Ephedrine, etc. These stimulate the radiating fibres of the iris, the heart, the blood vessels (except the coronary vessels), the sphincters of the alimentary canal and the bladder, and the uterus of some animals.

(*c*) *Those acting by directly stimulating the muscles* : Posterior Pituitary, Histamine, Barium and Lead.

II. Drugs which depress the involuntary muscles

Drugs which relax the spasm of different hollow organs are known as antispasmodics or spasmolytics.

(*a*) *Drugs which depress the parasympathetic nerve-endings* :

Atropine and its allies, Pethidine. These paralyse the circular m... of the iris, alimentary canal, bronchi and the urinary bladder.

(*b*) *Cholinergic drugs* : These dilate the arterioles.

(*c*) *Sympathomimetic drugs* : These depress the same group of muscles as those by parasympathetic depressants ; the mechanism however is different.

(*d*) *Those acting directly on the involuntary muscles* : Nitrites, Papaverine, Benzyl Benzoate, Pethidine, Volatile Oils. Caffeine and other purine derivatives dilate the vessels by acting directly on the muscles.

CLASS C : **Drugs which act on the cardiac muscle,** *see* page 279.

Therapeutics.—Affection of the muscles, both voluntary and involuntary, demands treatment. This may be characterised by either over-activity or diminished activity. Over-activity of the voluntary muscle is evidenced by convulsion, which may be clonic or tetanic and should be treated by drugs which will relieve convulsion, *i.e.* by bromides, chloral hydrate, cerebral sedatives, like phenobarbitone, phemitone, or in severe cases by the administration of general anaesthetics, like chloroform. Quinine has been found useful in *myotonia congenita.* Similarly, inactivity of the voluntary muscle is characterised by paresis or paralysis, and this requires administration of suitable drugs which increase either the nutrition of the muscle or tone or activity. For this purpose strychnine, neostigmine, physostigmine, guanidine, potassium salts and ephedrine are selected. The last five are used in *muscular dystrophies* which resemble in some respect curare paralysis, and these drugs possess anti-curare action. Pyridoxine hydrochloride (vitamin B_6) improves myasthenia gravis, muscular dystrophy, etc. Vitamin E is used in some cases of neuro-muscular paralysis, e.g. muscular dystrophies and nervous affections like amyotropic lateral sclerosis on the idea that these conditions may be due to deficiency of this vitamin.

A reduction of ionic calcium in the blood produces neuro-muscular hyperexcitability, e.g. tetany ; while an increase of serum calcium, temporarily or permanently, produces a corresponding degree of clinical improvement.

Spasmodic contraction of the involuntary muscles may be evidenced in different organs. Thus bronchial antispasmodics are used to relieve spasm of the bronchial muscles, as in asthma ; spasm of the vessels is relieved by nitrites, and that of the intestines and other organs like the bladder, by belladonna, atropine, papaverine and pethidine. For relief of paralysis or paresis of the intestine or bladder, carbachol, neostigmine and physostigmine are suitable remedies.

GROUP VII
DRUGS ACTING ON THE CARDIO-VASCULAR SYSTEM

Class A : Drugs acting on the heart

1. Cardiac tonics
   Digitalis, Strophanthus, Squill, Apocynum
2. Cardiac depressants
   Aconite

Class B : Drugs acting on the vessels

1. **Drugs raising the blood pressure**
   (*a*) Vaso-constrictors : **Adrenaline, Ephedrine, Amphetamine, Methedrine, Pituitary Extract, Ergot** (q. v.).
   (b) Drugs or Measures increasing blood volume ; *see* **Blood transfusion**
2. **Drugs lowering the blood pressure**
   (*a*) Vaso-dilators : **Amyl Nitrite, Octyl Nitrite, Nitro-glycerin, Sodium Nitrite. Spirit of Nitrous Ether** (see Diuretics), **Acetylcholine, Carbachol** (*see* page 235).
   (*b*) Drugs or **Measures** reducing the volume of blood : **Leech, Blood letting, Purgatives.**

CLASS A : Drugs Acting on the Heart

The real function of the heart is that of a pump and the efficiency with which this action is performed is of utmost importance both in health and disease. It is a peculiarly constructed nervo-muscular organ performing complex functions and is capable of originating spontaneous rhythmical movements from the impulses generated in the muscle itself—myogenic—and Gaskell describes as its functions, *rhythmicity*, *excitability*, *contractility*, *conductivity*, and *tonicity*.

By virtue of the excitability the heart muscle responds to external stimuli by producing contraction. But unlike other muscles it will not contract when the stimulus is too weak but if the stimulus is adequate the muscle will contract to its full ability, *i.e.* all or none. Unlike skeletal muscle the cardiac muscle will not respond to stimuli during the phase of contraction and this period during which the heart will not contract is known as the "refractory period." Conductivity is another property of the cardiac muscle ; this is specially developed in the bundle of His and its branches. Drugs which depress conductivity also diminish excitability. Another important characteristic of the heart muscle is its power to conserve energy so that it can readily increase its output several times when necessity arises. This is ordinarily known as "reserve force" as opposed to "rest force" which enables the heart to perform its function during bodily rest.

Though the muscular fibres spontaneously contract yet they are controlled and regulated by the nerve centres. Two centres control the cardiac mechanism, *viz.*, the cardio-inhibitor and the accelerator. Afferent impressions from various parts of the body, including the seat of mind and the heart, are transmitted to the centres in the medulla to be reflected to the heart. The vagus system consists of the centre, nerves, ganglia and nerve-endings, the chief function so far as the heart is concerned is that of restraint or inhibition. It begins at the centre whence the fibres pass to groups of cells in the heart-wall forming vagus ganglia, whence fibrils pass to the sino-auricular node (normal pace maker) in the auricle and to the bundle of His. Stimulation of any part of this system is followed by slowing or weakening of the heart beat with depression of conductivity and loss of tone, either by acting on the auriculo-ventricular bundle or by diminishing the irritability of the ventricle itself, or tonicity ; while depression results in increased frequency and strength of the beat and increased tone by making the heart free of the vagus influence. The accelerator nerves belong to the sympathetic system, and consist of centre, nerves, ganglia and nerve-endings. The

effect of excitation, besides increasing the rate, is to in-crease the force of contraction and conductivity. The vag (parasympathetic) and accelerators (sympathetic) are therefore antagonistic in their effects, and since they are in constant activity they form a sensitive balanced con-trol mechanism which favour prompt response to any influence.

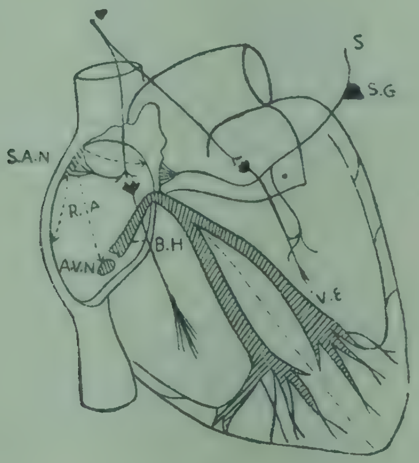


Fig. 15.—Innervation of the Heart, S.A.N., sino-auricular node. A.V.N. auriculo-ventricular node. B.H., bundle of His dividing into two branches ; one entering the right, the other left ventricle. V., parasympathetic fibres (vagus terminating round the ganglion cells in the auricles. V.E. vagal endings in th auricles and ventricles. S., sympathetic terminating round the stellate ganglion (S.G.), and the nerve fibres issuing from the ganglion end in auricles and ventricles (Modified from Wright's Applied Physiology)

The contraction of the heart is initiated in the sino-auricular node situated at the mouth of superior vena cava From here the wave of excitation passes over both the auri-cles to the auriculo-ventricular node, which is situated be-tween the auricles and the ventricles. From the auriculo-ventricular node the wave passes down the bundle of His to the endocardial surface of both ventricles. The bundle and its branches are composed of large fibres, which are termed Purkinje fibres.

In order that the heart may functionate properly it must have ample supply of oxygen and in this respect it differs from voluntary muscle in that it cannot function without supply of oxygen, *i.e.* it cannot enter into oxygen debt. Under normal conditions weight for weight this oxygen consumption is greater than any other tissue of the body. It receives oxygen from the coronary arteries and the efficiency of coronary circulation depends upon the heart's contraction. As long as the supply of oxygen is adequate the heart can utilise both carbohydrate and pro-tein to supply heat and energy and any decrease in oxygen will enable the heart to utilise glycogen to a limited amount

which it reduces to lactic acid, but is rapidly poisoned by it. Therefore any interference with coronary circulation at once injures the heart, and other things being equal slowing of the heart ensures better coronary circulation resulting in improved nutrition and recuperation.

The coronary arteries are supplied by the sympathetic and the parasympathetic vagus. The stimulation of the former dilates and that of the latter constricts the vessels. It follows therefore that both the blood supply to the heart and consequently its work are diminished by vagus stimulation and increased by sympathetic stimulation.

The maintenance of efficient circulation depends upon the condition of the heart muscle. Normally the different parts of the entire circulatory system are so adjusted that they facilitate the work of the heart, and any disturbance in any part of the circulatory chain entails extra work upon the heart muscle which asserts itself to meet the requirements of the body.

Two conditions intimately associated with heart disease require special mention, *viz.*, "compensation" and "auricular fibrillation."

Compensation.—The term is used to designate the degree of impairment of heart's activity, *i.e.* the ability of the heart to maintain efficient circulation against some leakage or other adverse condition. We speak of failure of compensation or heart failure, when the heart is unable to maintain it This inability is due to excessive strain on the heart muscle. For practical purposes Mackenzie differentiates two functions of the heart muscle. The one necessary to maintain efficient circulation when the body is at rest, which he calls "rest force," and the other called into action during an effort, however small, which he calls "reserve force." The first signs of heart failure are observed with the exhaustion of the reserve force, and if the strain continues without any repair or recuperation, true signs of heart failure appear, when the heart muscle is unable to maintain efficient circulation even during the period of rest. The signs of failure of compensation are dyspnoea, orthopnoea, weak and dilated heart, rapid pulse, sluggish peripheral circulation with cold extremities, oedema and dropsy.

Auricular flutter and fibrillation.—These terms are applied to two forms of disordered heart's action characterised by extremely rapid auricular beats. This is observed by electrocardiogram tracings. In fibrillation the auricular waves are irregular and have a rate of about 400 to 500 per minute. In flutter the waves are regular and have a rate of 250 to 300 per minute. In these conditions the bundle of His is incapable of conducting impulses at such rates and a variable degree of heart block is always

present so that the ventricular rate is about 100 to 1 per minute. In fibrillation there is complete irregulari of the pulse—no two beats being the same in force rhythm—and absence of signs of auricular contracti It is a serious complication, and occurs in almost all ca of heart failure and in old standing cases of mitral disea

Normally the wave of excitation originated at t sino-auricular node is followed by a refractory period, a the whole auricle remains in that condition till the wa is completed. In fibrillation the refractory period shortened and the wave of excitation becomes slow so th by the time the waves have travelled over the auri another part recovers (owing to shorter refractory perio and sends waves of excitation before the previous on have completed. Thus innumerable waves of excitati arise from abnormal parts of the auricle and travel rou and round producing what has been termed by Lew "circus movements." These irregular impulses pass in the ventricles which respond irregularly and inefficient at a rate far greater than their maximum capacity. A a consequence of this the ventricular muscles becor exhausted. Digitalis and quinidine are very useful in th condition.

Cardiac output.—The output of the heart depends largely on t venous return, and since muscular movements aid venous retu muscular exercise is the most efficient method of increasing cardi output. The cardiac output is only slightly increased by measu which will accelerate the heart, *e.g.* by adrenaline which stimula cardiac sympathetic, or by atropine. Although small doses of ad naline increase the output, large doses may actually reduce Digitalis ordinarily does not increase the cardiac output; in fa with prolonged slowing, as happens after over-digitalization, t total output per minute is considerably reduced though the outp with each systole is greater than normal. Digitalis increases t output of the heart in cases of congestive failure only but is different with moderate dilatation.

Most vaso-dilators, *e.g.* the nitrites, increase the output but the dilatation is great and the blood pressure falls, the output diminished.

Infusion of saline by augmenting the venous return also has tendency to increase the output.

Heart rate.—The rate of the heart may be affected in t following ways:—

A. Slowing of the rate may be caused

(*a*) *By acting on the vagal centre.*—Drugs which stimulate t central nervous system also stimulate the cardiac centre. But t effect on the vagal centre is more powerful than on the sympathet so that slowing of the heart results. The best example of stimu tion of the vagal centre is deficiency of oxygen in the blood happens in asphyxia. Aconite, digitalis, strophanthus, squill, co vallaria, picrotoxin, strychnine and morphine cause slowing by stim lation of the vagal centre. High blood pressure affects the medu and causes slowing of the heart, and any cause which will raise t blood pressure will produce slowing. This effect is only observ when the vagi are intact or not paralysed by atropine. Thus ad

[illegible] slowing during the period when the pressure is highest although it has no direct effect on the medulla. High blood pressure distends the aorta and the carotid sinus which sends afferent impulse to the cardiac centre and reflexly slows the heart. Pituitary extract also acts in the same way. Afferent impulses through the fifth and the tenth nerves reflexly stimulate the vagal centre, e.g. inhalation of **ammonia vapour.**

(*b*) *By acting on the ganglion cells.*—Nicotine, coniine, lobeline and gelsemium stimulate the ganglion cells in the course of the vagus and cause slowing. These are depressed subsequently and in large doses paralysed when the rate is accelerated.

(*c*) *By acting on the nerve-endings.*—Stimulation of the endings of the parasympathetic (vagus) causes slowing of the rate; e.g. by pilocarpine, acetylcholine, carbachol, physostigmine, and **members of the digitalis group.**

(*d*) *By acting on the cardiac muscle.*—Drugs alter the rate of the heart by their action on the muscle. Many drugs in small doses cause slowing, while in large doses produce quickening through their effects on the excito-motor portion of the heart (bundle of His). Barium, digitalis, quinidine, aconite and pituitary extract cause slowing by acting directly on the cardiac muscle.

B. Quickening of the rate may be caused

(*a*) *By acting on the sympathetic centre.*—Very little is known regarding the action of drugs on the accelerator centre. Cocaine stimulates the centre and causes acceleration of the heart. Excitement and anoxaemia increase the frequency of the heart's rate either by stimulating the sympathetic centre in the medulla or by stimulating the secretion of adrenaline.

Reflex stimulation, as by the application of counter-irritants, accelerates the heart, and any cause which lowers the blood pressure causes quickening of the heart by diminishing the tonus of the medulla.

(*b*) *By acting on the ganglion cells.*—Nicotine, coniine, lobeline and gelsemium cause acceleration in large doses by paralysing the ganglion cells in the course of the vagus.

(*c*) *By acting on the nerve-endings.*—Atropine, hyoscyamine and hyoscine cause quickening by paralysing the vagal nerve-endings, while adrenaline, tyramine, ephedrine, cocaine and pilocarpine in small doses cause acceleration by stimulating the sympathetic nerve-endings.

(*d*) *By acting on the cardiac muscle.*—Caffeine, digitalis in poisonous doses.

Cardiac stimulants.—These are drugs which maintain an efficient circulation, when the heart fails to perform its function, by improving its activity. Various causes may produce this condition: generally it occurs as a terminal event in many diseases. Since failure of the heart is often accompanied by failure of respiration, it is rather difficult to assess the value of a drug on the heart, as many drugs reputed to be cardiac stimulants act indirectly by stimulating the respiratory centre and thereby improving the oxygen supply to the heart (*see* **Analeptics**, page 218).

Cardiac stimulants may be classified as follows :—

1. *Those acting by stimulating the sympathetic nerve-endings* : Adrenaline, Ephedrine (small doses), Pseudo-ephedrine, Tyramine, etc.

2. *Those acting by paralysing the parasympathetic nerve-endings* : Atropine.

3. *Those acting by stimulating the medulla* : Leptazol, Nikethamide, Camphor, Strychnine.

4. *Those acting on the cardiac muscle directly* : Digitalis group of drugs, Caffeine.

5. *Those acting by improving the nutrition of the myocardiu*
(*a*) *By improving coronary circulation*: Theobromine, Th phylline, Caffeine, Adrenaline, Nitrites and Digitalis.

Nitrites also cause general fall of blood pressure, and if this great, may diminish the flow of blood through the coronary vess Digitalis causes constriction of coronary vessels, but this is observed in therapeutic doses, and causes increased flow of bl through them. *Glucose acts as a nutrient* to the cardiac muscle

(*b*) *By improving the condition of blood*: Iron and other h matinics, inhalation of oxygen.

The heart is stimulated reflexly by inhalation of ammon Alcohol, ether and ammonia also stimulate the heart reflexly fr the stomach.

Cardiac tonics are drugs which improve the action of the he by increasing the tone and nutrition of the cardiac muscle. Where cardiac stimulants are used as an emergency measure to tide o a critical period; cardiac tonics produce a more permanent eff These may act either directly on the muscle, possibly by giving re *i.e.* increasing the period of diastole and improving nutrition throu better coronary circulation, or indirectly by improving the gene health and the condition of the blood. Cardiac tonics acting direc are digitalis and its allies, caffeine, theobromine. Those acti indirectly are iron **and its salts.**

1. Cardiac Tonics

DIGITALIS FOLIUM

Digitalis Leaf. (Digit. Fol.)

Syn.—Foxglove Leaves.

Source.—Leaf of *Digitalis purpurea*, rapidly dried at a te perature of about 60°C. as soon as possible after collection.

Characters.—From 10 to 30 cm. or more in length, up to 4 to 10 cm. br with a winged petiole, ovate-lanceolate, subacute, crenate. Upper surface so what rugose, dull green, slightly hairy. Under surface paler, pubescent, w prominent veins. No odour. Taste, very bitter.

Composition.—The chief active principles of digitalis are seve *glycosides* which on hydrolysis split up into sugar and a non-sug component, *aglucone*. The aglucones are responsible for the di talis action, whereas the sugar helps penetration. They may grouped into two classes, *viz*:—

(*a*) *Alcohol soluble*

1. *Digitoxin*, crystalline. $C_{41}H_{64}O_{13}$. Represents the digitalis action. It the most abundant, active and most important constituent of the leaves (0.2 0.4 p.c.). It undergoes hydrolysis and forms an aglucone, *digitoxigenin* and sugar *digitoxose*. 2. *Gitoxin*. $C_{41}H_{64}O_{14}$, which also breaks up into *gitoxige* and sugar *digitoxose*. 3. *Digitalin*, amorphous. $C_{36}H_{55}O_{14}$. Occurs in leaves a seeds. Splits into dextrose, digitaligenin and digitalose. Produces typical digit effect; half as active as digitoxin.

(*b*) *Water soluble*

1. *Gitalin* and *digitalein* are mixtures of indefinite composition. 2. *Digi nin*, a saponin, occurs both in crystalline and amorphous forms. The crystalli form is less readily soluble in water. It helps the solution of digitoxin in wate

Digitalis Folii Pulvis. (Digit. Fol. Pulv.).—Powdered Digit lis Leaf.

Digitalis Praeparata. *Syn.—Powdered Digitalis.*—Prepar Digitalis is Digitalis Leaf reduced to moderately coarse powder, portion being rejected. Standardised by biological assay to conta 10 units in 1 gramme. 10 grs. contain 6 units of activity.

B. P. Dose.—1/2 to 1½ gr. or 30 to 100 mg. 1 Unit of activity in 100 mg.

OFFICIAL PREPARATIONS

1. Tabellae Digitalis Praeparatae. *Syn.—Digitalis Tablets.*—B. P. Dose. 1/2 to 1½ grs. or 30 to 100 mg. N. B. If the quantity contained in a tablet is mentioned, 1 gr. tablet **should be dispensed.**

2. **Tinctura Digitalis.**—No. 1 prepared from the leaf, and No. 2 from prepared digitalis. Contains 1 unit of activity in 15 ms. **B. P. Dose.—5 to 15 ms. or 0.3 to 1 mil.**

DIGOXINUM. $C_{41}H_{64}O_{14}$.—Digoxin is a crystalline glycoside obtained from the leaves of *Digitalis lanata*.

Characters.—Colourless, four or five-sided tabular crystals ; odourless ; taste, in dilute alcoholic solution, bitter. Almost insoluble in water, soluble in dilute acids.

B. P. Dose.—(Initial dose).—**1/60 to 1/40 gr. or 1 to 1.5 mg.** Maintenance dose.—**1/240 gr. or 0.25 mg.** once or twice daily. For intravenous injection initial dose.—1/120 to 1/60 gr. or 0.5 to 1 mg.

Official Preparations

1. **Injectio Digoxini.—B. P. Dose.—150 to 300 ms. or 10 to 20 mils.** intravenously. Contains 1/60 gr. of Digoxin in 300 ms.
2. Tabellae Digoxini.—B. P. Dose.—*Initial dose* :—**1/60 to 1/40 gr. or 1 to 1.5 mg.** *Maintenance dose* :—**1/240 gr. or 0.25 mg.** once or twice daily. N. B. If the quantity is not stated, 1/240 gr. tablet should be used.

Non-official Preparations

1. **Digitalin**—Under this name the following varieties are found—
(a) **Amorphous Digitalin** (*Homolle*).—Consists of mixture of glycosides. Insoluble in water. *Dose.*—1/60 to 1/30 gr. or 1 to 2 mg. in granules.
(b) **Crystallised Digitaline** (*Nativelle*).—Consists mostly of digitoxin. Is cumulative. *Dose.*—Granules 1/240 and 1/600 gr. (0.25 and 0.1 mg.). 1/600 gr. = 15 ms. of tincture or 1½ grs. powdered leaf.
2. Digitoxin, U. S. P.—In minute, white crystals. *Dose.*—1/600 gr. or 0.1 mg.
3. **Digalen.**—Contains the active principles of the leaves. 1 mil=150 frog units or 1 cat unit, *i. e.* 0.1 grm. digitalis pulverata. One tablet or ampoule=1/2 cat unit or 0.05 grm. digitalis praeparata. *Dose.*—5 to 15 ms. or 0.3 to 1 mil.
4. Pilulae Digitalis Co., B. P. C. *Syn. Guy's Pill.*—Powder digitalis, powder squill, pill of mercury, each 1 gr., syrup of liquid glucose *q. s.* for one pill. *Dose.*—1 to 2 pills.

Pharmacology

Locally.—Digitalis, owing to the presence of glycosides, powerfully irritates the mucous membrane and subcutaneous tissues causing inflammation and pain. This effect is more marked with digitoxin than with digitalin which is often used subcutaneously without causing any local irritation. Subcutaneous injection of digitoxin causes much pain and irritation and sometimes a sterile abscess.

Internally. **Gastro-intestinal tract.**—Small doses appear to have no action, but the glycosides and the saponins are sometimes irritating to the gastric mucous membrane. If continued long even in therapeutic doses it causes **nausea** and **vomiting,** due not to any local irritant effect on the stomach but to stimulation of the vomiting centre after absorption, or perhaps through stimulation of the sensory fibres of the vagus in the heart, which is a secondary manifestation of the cardiac action. In practice this should be regarded as a sign of over-digitalization. It is slowly absorbed from the intestine and is not affected by the digestive juices, but in case of venous engorgement, as happens in diseases of the heart, absorption is delayed and there is some destruction of the glycosides. The tincture and digitoxin however are quite easily absorbed and will manifest their effect on the heart in from four to seven hours. According to Cloetta, digitoxin is more resistant to digestive juices than other glycosides.

All the glycosides are readily absorbed when given p
rectum.

Heart and circulation.—Digitalis produces its princip
effects on the circulatory system. It **slows the rate of t
heart, prolongs the period of diastole, increases the for
of contraction,** and **improves the tone of the musc**
Before proceeding to describe its action on the differe
structures of the mammalian heart it will be convenie
to discuss its effects on the frog first, for it was in th
animal that its effects on the heart were first studie
Although the action of digitalis on the frog's heart
different to that on the mammalian heart it has be
pointed out that the reaction of human heart in diseas
condition approximates more closely to that of the frog
heart than to that of the mammalian organ (Cushny).

Frog.—If a tracing of the heart of a decerebrated fr
is taken and then an injection of digitoxin is given, a we
defined series of phenomena are observed. The systo
becomes more powerful and the heart becomes slow
from prolongation of the diastole. The increased contra
tion enables the heart to empty itself more complete
during the systole and the ventricles become more co
pletely filled through prolonged diastole. If the dose
increased the auriculo-ventricular conductivity is lower
and the rhythm is altered. There may be two or mo
beats of the auricle for each ventricular contraction,
there may be a long pause in diastole between a series
regular contractions. Finally, the ventricles may st
beating and remain standstill in the position of systo
whilst the auricle continues to beat. It is obvious that tw
changes take place in the frog's heart, *viz.*, (1) *change*
rhythm, and (2) *change in tone and contraction.* The
effects are due to direct action of the drug on the cardi
muscle since the same effects can be elicited after destru
tion of the central nervous system, or division of the vag
sympathetic fibres, or in the excised heart under atropin

Mammals.—The action of digitalis on the mammali
heart may be divided into three stages depending on t
preponderance of its effects either on the inhibitory mech
nism or on the cardiac muscle.

The first or therapeutic stage is characterised
moderate slowing through stimulation of the vagus cent
and increased contraction of the cardiac muscle resulti
in more complete systole. The output of the heart
thus increased while the slowing gives more time for t
ventricles to be better filled. As a result of this effect t
veins empty themselves more thoroughly into the hea
the venous pressure falls and the arteries get better fille
The arterial pressure first rises owing to the increas

ventricular force and greater output. If the dose is increased the arterioles contract from stimulation of the vaso-constrictor centre and from direct stimulation of the muscles of the vessels.

The second stage or that of poisoning is marked by overactivity of the inhibitory mechanism and the pulse becomes slower and irregular. The heart gets more time to fill, consequently the output with each systole is greater than normal. But since the rate is extremely slowed the total output per minute and the efficiency of the pumping action of the heart are less than normal. Moreover, owing to the inhibition of the conductivity of the muscles of the auriculo-ventricular bundle, the auricular impulses do not pass on to the ventricles, thus producing incipient or, less frequently, complete heart-block, *i.e.* the ventricles beat at a slower rate than the auricles, or the ventricle may adopt its own rhythm. Moreover, owing to the constricting effect on the arterioles, the renal vessels contract powerfully, and there is diminished secretion of urine from reduced blood flow through the kidney.

The third stage follows excessive doses and is hardly ever observed clinically in man. The heart muscle becomes extremely irritable and the ventricular rhythm becomes accelerated, but the nervous mechanism is not involved since the stimulation of the vagus may slow the rate. The auricular muscles are also affected and the combination of these effects gives rise to irregularity of the heart producing auricular-ventricular arrhythmia, spontaneous rhythm, extra-systole and finally fibrillation leading to failure of myocardium and the stoppage of the heart in diastole.

Digitalis produces all the above circulatory effects through its action on the following five structures :—

1. **The sino-auricular node.**
2. **The cardiac muscle.**
3. **The auriculo-ventricular** bundle.
4. **The coronary arteries.**
5. The systemic arteries.

1. By its inhibitory action on the **sino-auricular node** it causes a **slowing in the rate of the heart.** This effect is not so marked in therapeutic doses but is observed in toxic doses and may not be due entirely to digitalis action on the sinus node, but in part to stimulation of the vagus centre. Since very little slowing is observed after cutting the vagi or in an isolated heart, it is evident that this slowing is not due to its action on the vagal ending in the sinus node but is the result of stimulation of the vagal centre. This slowing is often a desirable therapeutic effect, but in certain conditions, *viz.*, old age, cardio-sclerosis, and in some infectious fevers, therapeutic

doses of digitalis fail to effect any such slowing. A seco effect of digitalis on this node is to interfere with regular rhythmic projection of impulses, so that **si arrhythmia** is set up, *i.e.* the heart rate shows regular alt nating short phases of acceleration and slowing. T effect is also due to stimulation of the vagus, and is checl by atropine or section of the vagi.

2. Digitalis acts directly on the **cardiac muscle,** its effect here is threefold, *viz.*—(1) it increases its tonic *i.e.* the heart remains in a state of partial contraction incomplete relaxation during the period of diastole ; t effect keeps the heart in readiness to respond at once stimulation ; (2) it increases its **contractility** ; and (3) renders it more **irritable,** *i.e.* increases its sensitiveness stimuli. The papillary muscles are also toned strengthened. The first two effects—*increase of tone* *contractility*—are more marked when the heart muscle damaged and therefore is of great value in all cases cardiac failure, but the third effect—*irritability*—if creased beyond the normal, as may happen in toxic dos may give rise to harmful symptoms such as premature c tractions, tachycardia, and fibrillation. By increasing excitability of the ventricular muscle, digitalis may ca further increase in the rate of fibrillation, or an incre of ventricular beats in cases of complete heart block.

Another important effect of digitalis, as observed electro-cardiogram, is an alteration in the T wave wh becomes inverted, and since this effect is not abolished the previous use of atropine it must be due to its dir action on the muscle.

In therapeutic doses the rhythm of the heart becon slower, the ventricles contract and become smaller empty themselves more thoroughly than they normally so that with each beat the ventricles expel more blood i the aorta and pulmonary arteries. The ventricu changes under digitalis consists in reducing the numl of beats and increasing the relaxation of the fibres fr inhibitory activity, and strengthening the systole fr direct action on the muscle, which also limits the per of relaxation without affecting the rhythm.

3. The function of the **auriculo-ventricular bundle** to conduct impulses from the auricle to the ventricle, that the ventricular contraction follows the auricular regularly, and the time taken for the passage of the i pulse down this bundle (A-V interval) is one-fifth of second. Digitalis may cause, through interference w this conduction (1) a prolongation of the A-V interval. (2) in toxic doses **incipient,** or less frequently even **co plete heart-block.** These effects, the first of which c only be ascertained by tracings, are toxic, and call for

stoppage of the drug. On the other hand this prolongation of the auriculo-ventricular interval makes it useful in the treatment of auricular fibrillation, so that digitalis blocks many of the auricular impulses to pass into the ventricle.

4. In therapeutic doses it is doubtful if digitalis has any constricting effect on the **coronary arteries.** The increased aortic pressure, the prolonged diastole, and greater contraction in systole resulting from therapeutic doses of digitalis lead to a vastly improved coronary circulation, with the result that the nourishment of the heart muscle is improved. In toxic doses, however, *coronary constriction* does occur, and this may cause such muscular weakness that the condition known as **pulsus alternans** may arise.

5. Small doses of digitalis have no direct action on the blood vessels, but toxic doses cause **constriction** of the **arteries**, partly by its action through the vaso-constrictor centre and partly by direct action on the muscle walls. The heart muscle being more sensitive to digitalis than the arterial muscle, the amount of digitalis which produces a definite effect on the vessels is fatal to the heart, and that *in therapeutic doses digitalis does not cause any arterial constriction and does not raise the general blood pressure.*

Temperature.—In medicinal doses it has no influence on the temperature, but in toxic doses it reduces it even in health. The effect is possibily due to increased activity of the heat controlling centre (Cushny).

Nervous system.—In medicinal doses it has no influence on the brain, the cord, and the sensory and motor nerves. In large doses it causes giddiness, headache, dimness of sight and disturbed hearing. Flashes of light, and a blue halo around bright objects also appear before the eyes. All these symptoms are probably due to some disturbance in the cerebral circulation. The reflex excitability and motor nerves are depressed only by toxic doses.

Digitalis stimulates some of the medullary centres. It stimulates the vagal centre causing slowing of the rate of the heart ; and stimulates the vaso-motor centre causing a rise of blood pressure (not observed in therapeutic doses). In toxic doses, or when continued long, it causes vomiting by stimulating the vomiting centre.

Kidney.—Digitalis is a powerful **diuretic** in **cardiac dropsies**, and the effect is proportional to the improvement in circulation. In dropsies not due to circulatory failure, it has little or no effect. It increases the quantity of urine secreted in normal animals but this is small and much less than what follows in cardiac dropsy. The fluid is more increased than the solids, although chlorides and uric acid

are increased which are correspondingly diminished in t blood. Diuresis is not due to any direct action on t kidney, but is produced through improvement in circul tion. According to Sollmann the following factors i prove renal circulation, *viz.*, (*a*) relief of venous pressur (*b*) increased output of the heart ; and (*c*) the hydraem resulting from the absorption of fluid from the oedemato tissues. If large doses are administered, the vaso-constri tion may be so great as to stop the excretion altogether.

Onset and duration of action.—Given by the mouth small therapeutic doses the effects appear very slowly, a it takes about 24 to 36 hours for the circulatory acti and 72 hours for the diuresis. But the appearance digitalis effect depends largely upon the dose. Thus wh full doses are given the effects appear within 2 to 4 hou and the maximum in 6 to 24 hours. Both digitoxin a digoxin get fixed in the heart muscle more firmly than a other cardiac glycoside, *e.g.* strophanthin, and once t fixation has taken place their removal is very difficult, fact they cannot be removed by any chemical or physi logical measure (Cloetta). This peculiarity of its acti makes digitalis so valuable therapeutically. Its products a eliminated from the cardiac muscle very slowly. It is for th reason that symptoms of poisoning may occur even thou the dose may not be increased, provided the drug is con nued for a prolonged period. Indeed therapeutic effec appear when an adequate concentration of the drug is pr duced in the blood and once established the effects contin for some time even after the stoppage of the drug.

Cumulative action.—Digitalis, when given for a lo time, sometimes shows symptoms of poisoning even wh its dose has not been increased. This is known as t cumulative effect of the drug, and is due to the retardati of its excretion or destruction. The danger of cumulati action has been exaggerated, for the symptoms disappe in a day or two after the use of the drug is discontinue The symptoms of excessive action are :—

1. Nausea and vomiting from stimulation of t vomiting centre. These are the first signs of toxicity a of full therapeutic effect.

2. A marked decrease in urinary secretion due constriction of the renal vessels.

3. Headache.

4. A progressive slowing of the pulse rate fro excessive vagus stimulation, which should never be allow to go below sixty.

5. The development of sinus arrhythmia, prematu contractions, dropped beats (incipient heart-block) fro depression of A-V bundle, extra-systole, tachycardia a fibrillation from hyperexcitability of the cardiac musc

In fact any form of cardiac irregularity may follow digitalis administration, and it becomes rather difficult to differentiate whether the irregularity is the result of digitalis treatment or a part of the clinical picture.

When any of the above symptoms arise the administration of the drug should be at once stopped.

Elimination.—It is chiefly excreted by the kidneys and partly by the gastro-intestinal mucous membrane. But its elimination is very slow often slower than its absorption, and its long continued use may cause cumulative effects.

Therapeutics

Valvular diseases of the heart.—Digitalis is a valuable drug in diseases of the heart. It is of supreme value in those conditions of the heart which have departed most widely from the normal. If the muscles are healthy but otherwise over-worked, exhausted and fatigued, digitalis by its effect on the cardiac muscle will restore its tone. In valvular diseases of the heart, where the incomplete emptying has caused the ventricles to dilate and there is an over-increasing strain on the muscle, digitalis has a wonderful influence in restoring the dilated and weakened ventricle to a state of efficiency. Under its use quick, weak and irregular contractions become slower, stronger and regular. As the diastole is prolonged, the heart gets more time for nutritive repair, and for more efficient subsequent contraction from the flowing in of more blood from the dilated auricle. Since digitalis acts by its effects on the cardiac muscle, it is of greater value in ventricular than in auricular dilatation. It therefore relieves dyspnoea, cough, venous engorgement of the lungs and of the abdominal organs, oedema, dropsy, and many other symptoms due to mitral regurgitation.

Digitalis is a valuable drug in **congestive heart failure**, whether mild or severe, whether the blood pressure is high or low, whether the heart rate is quick or slow, or whether aortic regurgitation is present or not ; although it is generally more useful in mitral than in aortic cases. The object of using digitalis is to relieve or prevent the characteristic symptoms associated with the two leading syndromes of myocardial insufficiency, namely, congestive or dyspnoeic failure. In the early stage of aortic regurgitation digitalis was considered useless or even dangerous as it was believed that by prolonging the diastolic interval it will allow more blood to flow back from the aorta and thus produce syncope. In most cases however the period of diastole is not prolonged and clinical evidence shows that in some cases of aortic valve failure digitalis often increases the cardiac reserve. In all cases it is desirable to

keep the patient in bed during this treatment. When th ventricle dilates, and the auriculo-ventricular orifice e larges, producing secondary mitral regurgitation wit symptoms of congestive heart failure digitalis is of gre value. By giving small doses its effect on the hea muscle may be obtained with relatively little change the rate.

Another great field of usefulness of digitalis is **cardiac irregularities.** It is of great value in **auricul fibrillation** which occurs in advanced myocardial and va vular lesions. In this condition the over-stretched aur cular muscles are unable to make concerted contractic and the auricle is kept in continual inco-ordinate activit These numberless irregular impulses pass into the ve tricle and the ventricle responds without any regularit in rhythm or strength. The action of digitalis in th condition is striking. Fifteen to thirty minims, three four times a day, should be given at first, and if the fibr llation is permanent, it should be followed by smaller dos once or twice a week, or once a day for some time. It ac by impairing the conductivity of the auriculo-ventricul bundle, *i. e.* by establishing partial heart-block, whereb many of the superfluous auricular impulses are block and do not pass to the ventricles.

Digitalis is also of great value in **auricular flutte** In this condition the auricle is also the seat of abnorm excitation and beats at a very rapid rate though regularl Given in full doses, digitalis will change the flutter in fibrillation and by reducing the conductivity of the bund of His will make the ventricles beat slowly.

Digitalis is contra-indicated in **partial heart-block** it tends to increase the degree of block. But opinio differ regarding its use in complete heart-block, inde some authorities recommend it on the ground that by slov ing the rate of the auricle and increasing that of th ventricle it will help to bring the auricular and ventricul rates more nearly together. It is to be avoided in *bundl branch block* and in *sino-auricular block.*

Other cardiac diseases.—Digitalis is of little or no valu in conditions of the heart with fibrous or fatty degeneratio i.e. in cardio-sclerosis. The heart muscle being partiall replaced by non-contractile tissue does not respond to th drug. It is better to avoid its use in these conditions as th over-worked muscle is readily poisoned. In acute myoca ditis or endocarditis it should be used with caution it may lead to dangerous overstrain of the hypersensitiv muscle. Although digitalis does not cause coronary co striction in therapeutic doses and that in patients with hea failure restoration of efficient action of the heart may in prove coronary circulation, it is not indicated in angi

pectoris unless there are signs of heart failure. Cases are on record where digitalis actually increased the frequency of anginal attacks. The heart injured by diphtheria toxin is more susceptible to digitalis and its use may cause further damage. If congestive failure is present in diphtheritic hearts, digitalis should be used with caution and in smaller doses. In fact digitalis has no influence in protecting the heart against diphtheria toxin. Its administration leads to rapid disappearance of the congestion of the base of the lungs which follows an attack of pneumonia, bronchitis, etc.

Digitalis as a diuretic.—Digitalis is the most reliable and often successful diuretic in **cardiac oedema,** and the majority of cases require no further medication. Remarkable results follow rapid digitalization, although the changes in the rate of the heart and occurrence of diuresis may not necessarily run together. Since digitalis causes constriction of vessels, including those of the kidneys, in large doses, massive doses do not necessarily act more efficiently though the effects are often more dramatic. It also acts as a diuretic in **nutritional** and **anaemic oedemas** where the circulation is impaired. It is however of not much use as a diuretic in dropsies from other causes, *e.g.* in Bright's disease. But in chronic Bright's disease when the anuria is the result of deficient circulation, digitalis, especially the Guy's pill, is of great service. Since therapeutic doses do not materially alter the blood pressure, high arterial pressure *per se* is no contra-indication to the use of digitalis.

Acute febrile diseases.—Digitalis is often used in different febrile diseases where the heart becomes affected from the toxins of the infection or from high temperature. In these conditions digitalis may be used to improve the tone of the heart and produce slowing of its rate. Its use has also been advocated in pneumonia, but the different factors such as high temperature, toxins, or the invasion of the heart with specific organisms exert an influence over the heart which digitalis cannot overcome. It has therefore been suggested that it should be used from the very commencement on the idea that if digitalization of the heart is done early it will prevent the toxin from affecting the heart. It is however debatable whether early digitalization will reduce the case mortality.

Digitalis and Calcium.—Calcium reinforces the action of digitalis on the myocardium and an *intravenous* administration of calcium in patients already digitalized caused death, but not in patients who received digitalis after administration of calcium. It is possible that calcium promptly adds to the digitalis effect already present,

whereas when given before digitalis, the slow action digitalis obviates any bad effect.

Caution.—It should be remembered, while treati cardiac disturbances, that the effect of digitalis varies different classes of cases ; that while it is of great valu in certain diseases of the heart, its effects are not marked in others, and in a third class of cases its use contra-indicated—being harmful or dangerous. Great ca and caution should therefore be observed in the selecti of cases for the exhibition of digitalis. The best way avoid any untoward effect during a course of digital treatment is to suspend the administration of the drug f a few days as soon as the physiological reaction is reache as evidenced by slow pulse, nausea, vomiting, and diarrhoe In this way the cumulative action is avoided. Cases sudden deaths are on record when the drug has bee pushed without stoppage after it had affected the heart

It is contra-indicated in partial heart-block, cerebr haemorrhage, embolism of recent origin and aort aneurism in its later stages ; and should be used wit caution in pronounced arteriosclerosis.

Prescribing hints.—The effect of digitalis in cardiac disorders shown by slowness of the rate of the heart and diuresis, and the are produced in therapeutic doses before any toxic effects—nause vomiting, coupled beats—are observed. Digitalis is best prescrib in the form of tincture, which should be given alone in 15 to 30 m doses three times a day to be diluted with water before takin because the tincture does not maintain its strength long when ke diluted in water. In any event it should not be administered mo frequently than at six-hourly intervals as it ordinarily takes s hours to get absorbed from the stomach. This dose should pushed till a definite response is observed in either the pulse, th urine, or the nausea, when its use should be stopped and the hea rate carefully watched. When the heart rate shows signs of i crease, half the dose should be given and the dose regulated occasion arises aiming to maintain compensation and keeping th pulse to about 80, with the smallest possible dose. It should noted that practically no therapeutic effect is produced until th total dosage nearly approaches the toxic and as a rule no benefici effects are observed till the second or third day. It has therefo been suggested that in urgent cases, a single large dose followe by smaller doses, until some definite response is obtained, should preferred. Since about 20 ms. of the tincture is destroyed a excreted in twenty-four hours, it is only necessary to give th amount daily as a *maintenance dose* after the patient has bee digitalized.

The other method of giving digitalis is that of Eggleston. H gives 7.5 mils of the standardised tincture per 100 pounds of bod weight (1½ ms. per pound) as the first dose ; followed in six hou by one fourth of the total dose, then smaller fractions every fo or six hours till full response is reached. With this method th effects appear within 2 to 5 hours after the first dose, reaching i maximum within 24 hours. This effect may continue for 14 to days without further administration. Much care and caution necessary when using digitalis in such large doses and unless one certain that the preparation is properly standardised such lar doses should not be used. Moreover, one should ascertain wheth

the patient had digitalis treatment within a fortnight before giving such large doses.

Irritation of the stomach is a great drawback to digitalis administration, when *parenteral administration* becomes necessary. Digoxin may be used intravenously like ouabain or strophanthin and will often produce quick effect ; but great care is necessary in giving digoxin intravenously, and the standard method of administration should be by the mouth. Given by the mouth the effects are observed within an hour and is very useful in auricular fibrillation. Given intravenously the effects are observed within 5 to 10 minutes reaching its maximum in one to two hours. But it should only be given when an extremely rapid action is necessary or when there is severe vomiting. Solutions for intravenous injection should be prepared immediately before use by mixing 1 mil of the injection of digoxin with 9 mils of injection of sodium chloride. The injection should be given slowly, taking 3 to 5 minutes, care being taken that no fluid leaks into the surrounding tissue.

Rectal administration is done in doses of 60 to 120 ms. of the tincture daily when vomiting prevents administration by the mouth. It should be diluted with 2 to 3 ozs. of 5 p.c. glucose saline solution and injected once daily. The effect becomes evident in one to two days.

Since these glycosides undergo decomposition and form resin-like bodies when kept in solution for long, old preparations, are useless therapeutically and may be harmful.

Diuresis generally follows the administration of digitalis in cases of heart failure, and if there is no diuresis, the use of the drug will not produce any beneficial results. In fact the secretion of urine is not increased unless there is oedema present, although digitalis may be given even in massive doses.

Though incompatible with iron on account of the tannin it contains, digitalis is often advantageously given with iron ; but the resulting inky mixture should be cleared by the addition of diluted phosphoric acid.

Lanatoside C., U.S.P.—It is a glycoside obtained from the leaves of *Digitalis lanata.* In colourless, white crystals or as white crystalline powder.

Dose.—1/120 gr. or 0.5 mg. (orally).

It is rapidly destroyed in 72 hours and is therefore not cumulative. May be administered intramuscularly or intravenously. It is less toxic than *Digitalis purpurea* and may be used in persons who show intolerance to other digitalis preparations.

Digilanid. (Not official).—Contains a mixture of amorphous closely related glycosides of *Digitalis lanata*, Lanatoside A, B and C, in the proportion of 46 p.c., 17 p.c. and 37 p.c. Valuable in cardiac failure either with normal rhythm or auricular fibrillation. Intravenously in 4 c.c. (2.6 mg.) doses.

STROPHANTHUS

Strophanthus. (Strophanth.)

Syn.—Strophanthus Seeds.

Source.—The dried ripe seeds of *Strophanthus kombe*, freed from the awns.

Characters.—Lanceolate to linear lanceolate, acuminate, about 12 to 18 mm. long, 3 to 5 mm. broad, blunt base, tapering apex, sides flattened, one side having a median ridge and the other being convex covered with silky appressed hairs. Characteristic odour. Taste, very bitter.

Composition.—It contains from 7 to 10 p.c. of a mixture of glycosides, K-strophanthoside, together with about 25 p.c. of fixed oil. K-strophanthin consists of cymarin, K-strophanthin-β and other glycosides, and yields on hydrolysis aglucone, strophanthidin, cymarose, and a sugar. *Choline*, oil and resin.

Strophanthus Pulvis. (Strophanth. Pulv.).—Powdered Strophanthus. Greenish-yellow with brown specs.

Official Preparation

1. **Tinctura Strophanthi.**—It is equivalent in activity to a 0.42 p. c. solution of the International standard Ouabain. **B. P. Dose.—2 to 5 ms. or 0.12 to 0.3 mil**

Ouabainum. (Ouabain.). **Syn.**—Strophanthin-G.—$C_{29}H_{44}O_{12},8H_2O$.—Ouabain is a crystalline glycoside obtained from the seeds of *Strophanthus gratus*, or from the wood of *Acokanthera Schimperi.*

Characters.—Small, colourless crystals, or a white crystalline powder ; odourless ; taste, bitter. *Soluble* in about 100 parts of water ; in dehydrated alcohol ; almost insoluble in solvent ether and in chloroform.

B. P. Dose.—1/500 to 1/240 gr. or 0.12 to 0.25 mg. By intravenous injection.

Official Preparation

1. **Injectio Ouabaini.—B. P. Dose.**—By intravenous injection.—**1/500 to 1/240 gr.** or **0.12 to 0.25 mg.** N.B. If no dose is stated, 1/240 gr. in 15 ms. should be supplied.

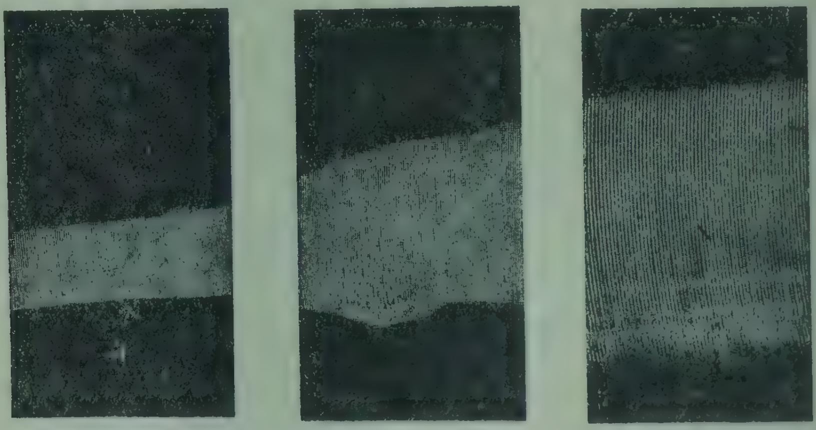
Strophanthinum, B.P.C. (Not official). **Syn.**—Strophanthin-K.—It is a mixture of glycosides obtained from strophanthus. Moderately soluble in water, and in alcohol (90 p.c.).

Dose.—1/240 to 1/60 gr. or 0.25 to 1 mg. ***by intramusculdr or intravenous injection.***

Pharmacology

Locally.—Strophanthin is an irritant to the mucous membrane, but less powerful than digitalis glycosides. On the other hand it has an anaesthetic action on the conjunctiva and cornea.

Internally. **Gastro-intestinal tract.**—Strophanthus is absorbed less rapidly than digitalis and does not produce any local irritation to the same extent as digitalis, it is also easily destroyed by the digestive juices, and loses much of its effects when given by the mouth.



A B C

Fig. 16.—Effect of Strophanthin on Isolated Rabbit's Heart Perfused with Locke's Solution.

At A strophanthin 0.2 mg. was given ; note—the heart acts more powerfully, the contractions become stronger. Figure B shows the effect after 15 minutes and the figure C, 30 minutes after B.

Heart and circulation.—Action exactly *similar to that of digitalis.* It does not cause constriction of the systemic

arteries in poisonous doses. As compared to digitalis it is poorly absorbed, more toxic to the heart, destroyed and excreted rapidly, therefore not cumulative.

Kidneys.—It is a diuretic in a normal person, and as it raises the blood pressure without constricting the peripheral renal vessels it sends more blood through the kidney and acts as a more efficient diuretic than digitalis. Like other glycosides it is partly destroyed in the body and is readily excreted from the heart muscle and therefore its action is short.

Therapeutics

Strophanthus is probably the most useful drug in the treatment of cardiac decompensation. Its only disadvantage is that when given by the mouth the glycoside is decomposed in the alimentary canal and its effects are uncertain. Ouabain (Strophanthin-G) being soluble in water and more uniform in composition is largely used intravenously and often in combination with glucose. It is valuable in severe acute decompensation, specially when associated with cardiac asthma and pulmonary oedema ; in acute heart failure following infectious disease; after paroxysmal tachycardia or extreme degrees of flutter-arrhythmia; when digitalis causes nausea or vomiting; as an alternative to digitalis in many cases of complete auriculo-ventricular block with bradycardial ventricular autonomy; and when insufficiency appears to affect the left more than the right side of the heart. This method however is not suitable where a prolonged treatment is necessary when digitalis will be found more convenient. With digitalis the effect of gradual absorption is more beneficial to the heart than the daily use of the intravenous injection. Ouabain is twice as potent as Strophanthin-K.

The advantages of strophanthin over digitalis are :—(*a*) Effect is quicker, being produced in a few minutes ; digitalis given by the mouth takes several hours, often two or three days to produce the full effect ; (*b*) a prolonged improvement of systolic activity, without prolonging the diastole which digitalis often causes ; and (*c*) the absence of cumulative effect.

SCILLA

Squill. (Scill.)

Source.—The bulb of *Urginea scilla*, divested of its dry membranous outer scales, cut into slices, and dried.

Characters.—In curved, very pale yellow, somewhat translucent strips, tapering towards both ends, from 0.5 to 5 cm. long ; pulverisable when dry, not when moist. Taste mucilaginous, bitter.

Composition.—A crystalline glycoside *Scillaren A*, $C_{36}H_{52}O_{13}$ and an amorphous soluble glycoside *Scillaren B*. The former on hydrolysis yields the aglucone scillaridin and rhamnose.

Scillae Pulvis. (Scill. Pulv.). Powdered Squill.—White or yellowish-white.

B. P. Dose.—1 to 3 grs. or 60 to 200 mg.

Official Preparations

1. **Acetum Scillae.**—10 p. c. **B. P. Dose.—10 to 30 ms. or 0.6 to 2 mils.**
2. **Oxymel Scillae.**—Active constituents equivalent to 5 p. c. w/v of squill. **B. P. Dose.—30 to 60 ms. or 2 to 4 mils.**
3. **Syrupus Scillae.**—Equivalent to 4.5 p. c. w/v of squill. **B. P. Dose.—30 to 60 ms. or 2 to 4 mils.**
4. **Tinctura Scillae.**—Equivalent to 10 p.c. w/v of squill. **B. P. Dose.—5 to 30 ms. or 0.3 to 2 mils.**

Pharmacology

Squill acts like digitalis in many respects. The description of the latter will therefore apply to that of the former with the following characteristics :—

1. Its action on the heart is almost the same as digitalis and when given intravenously it causes a greater rise of blood pressure ; but administered by the mouth its absorption is slow and less complete and therefore its effect on the heart is not so marked.

2. It is a *more powerful gastro-intestinal irritant than digitalis*, causing nausea, vomiting, purging (even bloody stools), and intense inflammation of the mucous membrane in full doses, and occasionally in medicinal doses. In many cases however this irritant effect is not observed.

3. It is an *expectorant* acting reflexly through gastric irritation.

4. It is a *more powerful diuretic* than digitalis. It acts in two ways :—(*a*) Like digitalis by improving the circulation, and (*b*) the active ingredient scillaren being excreted by the kidneys directly stimulates the renal cells.

Therapeutics

Squill may be used in cardiac and other forms of **dropsy.** But its irritant properties are somewhat mitigated when it is combined with digitalis. Even then it is safe to occasionally suspend its administration for a while. Guy's pill (page 283) is an excellent combination, and a efficient diuretic in **cardiac dropsy.**

It is rarely prescribed alone and is contra-indicated in acute renal disease or if there is gastro-intestinal irritation.

It is largely used as an expectorant, but should not be given in acute bronchitis. It is of great value in old standing pulmonary diseases where, besides acting as an expectorant, it tones up the heart the right side of which is so frequently dilated. In the chronic bronchial affections of children, the oxymel or syrup is always serviceable in 10 to 15 ms. doses, but its indiscriminate use in all varieties of bronchial affections is to be deprecated.

APOCYNUM. (Not Official). Syn.—Canadian Hemp.—Root of *Apocynum cannabinum*. It contains the glycoside *cymarin*, to which its action is due. It hydrolyses into *cymarose* and *strophanthidin*.

Dose.—1 to 5 grs. or 0.06 to 0.3 grm. of powdered root.

Non-official Preparation

1. Tinctura Apocyni.—1 in 10. *Dose.*—5 to 10 ms. or 0.3 to 0.6 mil.

Action and Uses.—Apocynum is a gastro-intestinal irritant in large doses, giving rise to nausea, vomiting and purging.

It possesses all the properties of digitalis on the circulation but the effects on the vaso-constrictor mechanism are relatively strong and it is not cumulative. It directly stimulates the unstriped muscles. It is a powerful **diuretic** and is largely used in **cardiac** dropsies. It is also recommended in dropsies due to cirrhosis of the liver and is also useful in causing the absorption of **pleuritic effusion.**

2. Cardiac Depressants

Excepting the central nervous system the heart is more liable to be affected by poisonous drugs than any other tissues of the body. When the heart is depressed, the force of contraction becomes less strong, the conduction is diminished, and the rate is reduced. Quite a large number of drugs act as cardiac depressants. They may be **classified as follows :—**

1. *Acting by stimulating the vagus centre* : Aconite, Morphine.
2. *Acting by stimulating the vagal nerve-endings* : Cholinergic drugs (*see* page 232).
3. *Acting by diminishing coronary circulation* : Pituitrin, Adrenaline (small doses).
4. *Acting directly on the cardiac muscle* : Aconite, Emetine, Quinidine, Hydrocyanic Acid, Chloral Hydrate and large doses of other organic hypnotics.

ACONITUM

Aconite. (Aconit.)

Syn.—Monk's Hood. *Katbis*, *Dudhiabish*, Hind.

Source.—Dried root of *Aconitum Napellus*.

Characters.—Dark brown, obconical ; usually 4 to 10 cm. long, from 1 to 3 cm. wide at the crown, to which is attached the base of stem or the remains of a bud and showing root scars. Internally, starchy, showing a stellate cambium. Odour slight ; taste slight, followed by a persistent tingling and numbness.

Composition.—(1) *Aconitine* (acetylbenzoyl-aconine), the chief active principle. (2) *Picraconitine* (**Benzoyl-aconine**). (3) ***Aconine***. (4) ***Aconitic acid*** and starch.

Aconiti Pulvis. (Aconit. Pulv.).—Powdered Aconite. Greyish-brown.

Official Preparation

1. **Linimentum Aconiti.**

Non-official Preparations

1. Tinctura Aconiti. I.P.L.—Contains 0.140 to 0.166 mg. aconitine per mil. **Dose.—5 to 10 ms. or 0.3 to 0.6 mil.**
2. Linimentum Aconiti, Belladonnae et Chloroformi. B.P.C. *Syn.*—*A.B.C.* Liniment. **Aconite, Belladonna and Chloroform liniment, equal parts.**

Pharmacology

Externally.—When applied to the skin rubbed up with chloroform or some fatty substance aconite first stimulates then paralyses the terminations of the sensory nerves.

thereby causing tingling, numbness and anaesthesia. It is rapidly absorbed from all mucous surfaces.

Internally. **Gastro-intestinal tract.**—The same tingling, numbness and anaesthesia are produced when aconite is applied to the tongue, followed by salivation caused reflexly through irritation of the nerve-endings of the tongue and nausea. In large doses it causes gastro-intestinal irritation such as nausea, vomiting and diarrhoea.

Heart and circulation.—In small doses it makes the heart slow, diastole is prolonged and the systole is weakened. The pulse becomes weak and soft and, if the dose is not increased, does not become irregular. The slowing is due to stimulation of the vagal centre and does not occur if the vagus is cut. Large doses directly affect the heart muscle and the heart becomes feeble, irregular and accelerated, auricular-ventricular arrhythmia being set up and finally the ventricle passes into fibrillation and the heart stops in diastole. These effects of aconite cannot be elicited in man in therapeutic doses and are due to the direct action on the cardiac muscle. The **blood pressure falls** from lessened output from cardiac depression in the early stage and later from paralysis of the vaso-motor centre.

Respiration.—In small doses it stimulates the respiratory centre, and breathing becomes deep and frequent, but it is soon followed by depression when the respiration becomes slow, deep, irregular and laboured. It is possible that some of the effects are reflex through vagus effects in the lungs. Death takes place from **asphyxia** due to respiratory failure from paralysis of the centre.

Temperature.—A febrile temperature is lowered by aconite ; the mechanism of this effect is not well understood, but increased diaphoresis is one of the factors.

Nervous system.—Whether applied locally or taken internally, aconite first stimulates and then depresses the periphery of the sensory nerves. The ends of the motor nerves are also somewhat stimulated and then depressed, and the nerves conveying thermic sensation are affected in poisoning. It first stimulates but soon depresses the vagal, vaso-constrictor and respiratory centres. The brain remains unaffected. The pupils first contract, then dilate. Large doses first stimulate and then depress the motor centres in the spinal cord. The convulsions observed in poisoning are due to asphyxia.

Skin.—Perspiration is increased possibly due to dilatation of the vessels of the skin. It sometimes gives rise to an erythematous rash.

Elimination.—It is mostly excreted in the urine, although traces of the active principle have also been detected in saliva, gastric juice, bile and sweat.

Acute toxic action.—Within a few minutes after swallowing a poisonous dose of aconite severe tingling and burning followed by numbness are noticed in the mouth and gullet. Intense abdominal burning; excessive salivation; vomiting and diarrhoea; cold, clammy skin and profuse sweating; tingling, formication, and numbness of the skin; small, feeble, irregular pulse; fixed, staring eyes; pupils first contract and then dilate; difficult respiration; muscular weakness; prostration; fainting; sometimes convulsions; lastly death either from asphyxia or occasionally from syncope. Consciousness remains, more or less clear, till death.

Treatment.—Emetics, pump, stimulants, hot bottles, friction, sinapisms to the heart. Tinct. digitalis 20 to 30 ms.; atropine 1/50 gr. to check vagus activity and to relax the bronchial muscles.

THERAPEUTICS

Externally.—Aconite in the form of a liniment is applied for the relief of pain in neuralgia, sciatica, muscular rheumatism and inflammatory joint affections. The addition of chloroform increases the efficacy, as it facilitates absorption. For this reason, the A. B. C. liniment is more effective than the B. P. preparation.

Internally.—Aconite is not used now in fevers as formerly except in inflammatory fevers in the early stage. Careful observation by Mackenzie and Price failed to elicit any slowing of the rate of the heart with aconite.

CLASS B: **Drugs acting on the vessels**

The arteries are elastic nervo-muscular tubes, whose calibre constantly changes owing to a variety of influences, which are transmitted by the vaso-constrictor and vaso-dilator nerves, from the vaso-motor centre located in the medulla, and certain subsidiary vaso-motor centres in the spinal cord. The arterial muscles are kept in a constant state of contraction or tone, which enables them to counteract the pressure of the fluid within. This tone is chiefly due to continuous reception of subminimal impulses from the vaso-constrictor centre. The vaso-dilators differ from the constrictors in that they are not in tonic activity, and that they produce dilatation by inhibiting the contractile impulses, the arteries having no dilator muscles. Both the constrictors and dilators belong to the autonomic system, and when both sets are stimulated the constrictor effect predominates, but if the stimulation is prolonged, the constrictors are the first to show signs of exhaustion, so that eventually there is dilatation.

The vaso-motor system may be influenced by drugs acting upon any part from the centre to the nerve-endings, and also reflexly by afferent impulses coming to the centre from other parts of the body. It should be noted however that some of the arteries—the pulmonary and cerebral—have no vaso-constrictor nerves. But the maintenance of sufficient cerebral and coronary circulation is most essential.

as on these depend activities of the vital centres in th medulla and of the heart.

By the *blood pressure* is meant the pressure to whi the walls of the arteries are subjected. The rise and fa of the blood pressure depend upon the activity of the vas constrictor and vaso-dilator nerves respectively. Beside the afferent influences affecting the pressure there ar other circumstances which greatly modify it. They ar (1) the heart's output in a given time ; (2) the total quan tity of blood in the circulation ; (3) the peripheral resis tance ; and (4) the viscosity of the blood.

The pressure may be raised by (1) general constric tion of the arterioles ; (2) increase in heart's output ; (3 increased volume of blood ; and (4) slightly by increase viscosity of the blood. The pressure is lowered by th opposite conditions.

The arterioles, specially those of the splanchnic area are the most important regulators of the arterial pressur so that when these arterioles dilate so much blood passe into them that no blood is left for the brain and other vita organs, thus causing faintness and even death. Eve when the arterioles remain contracted the pressure can not be maintained if the heart fails, or if there is muc loss of blood.

Capillaries.—Since the normal exchanges between th blood and the tissues take place through the capillary walls maintenance of efficient capillary flow is an importan function of the circulatory organs. The arterioles bein actively contractile act as flood-gates and regulate th amount of blood passing through any given set of capilla ries. The capillaries themselves are capable of contrac tion and dilatation and are controlled by chemical an nervous stimuli, and though controlled by sympathetic ar not affected by adrenaline beyond a certain distance fro the arterioles. Pituitary is supposed to contain hormone which maintains the normal tone of the capilla ries. Histamine, arsenic and antimony dilate the capilla ries. Dilatation of the capillaries of the splanchnic are is also the cause of fall of blood pressure in surgical shoc

Carotid Sinus.—This is the name given to the speciall innervated part of the vessels and tissues in the neighbou hood of the bifurcation of the common carotid into i branches and the carotid body, which is related to th carotid sinus. Recent studies by different observers hav elucidated its importance in the regulation of circulati and respiration. It has been pointed out by Heymans th the regulation of blood pressure through adrenaline secr tion is controlled reflexly by the sinus nerves whic normally exert a tonic inhibitory influence on the vas motor centre. Stimulation of the sinus electrically or b

stretching its walls by pressure from within provokes a combined reflex of cardiac inhibition and fall of blood pressure just in the same way that follows the stimulation of the central end of the vagus. A rise of pressure in the sinus inhibits and a fall of pressure in the sinus stimulates adrenaline secretion. During rest the sinus nerves exert a tonic inhibitory influence over adrenal activity.

A. Drugs or measures which raise the blood pressure

1. *Acting by stimulating the vaso-motor centre.*—All drugs which stimulate the central nervous system also stimulate the vaso-motor centre in the medulla. They cause a rise of blood pressure by constricting the vessels of the splanchnic area. The drugs belonging to this group are strychnine, caffeine, digitalis, camphor, atropine, cocaine, and so-called analeptics, leptazol, nikethamide, picrotoxin. Alcohol given in concentrated solution stimulates the vaso-motor centre reflexly and causes a rise of blood pressure. After absorption the splanchnic vessels dilate and there is a fall of pressure. Excess of carbon dioxide in the blood, as happens in asphyxia, also stimulates the centre. The centre may be reflexly stimulated by counter-irritants, which cause stimulation of the sensory nerves and vaso-constriction.

2. *Acting on the vaso-constrictor sympathetic ganglia.*—Nicotine, lobeline and coniine. They first stimulate when the pressure rises and then depress the ganglion cells.

3. *Acting on the vaso-motor nerve-endings.*—The normal tone of the vessels depends upon the activity of the adrenal glands, and removal or disease of these glands is followed by fall of pressure. Adrenaline, ephedrine and ergotoxine (in small doses) cause powerful vaso-constriction and a rise of pressure by acting on the sympathetic nerve-endings. Ergotoxine however causes subsequent depression and paralysis of the augmentor nerve-endings of the sympathetic and causes a fall of pressure.

4. *Acting on the arterial muscle.*—These, when administered either by the mouth, or as injection, cause vaso-constriction by acting on the muscles of the vessels. They are digitalis, posterior pituitary extract and barium. Digitalis however causes vaso-constriction in doses toxic to the heart, and its therapeutic administration is not followed by any such action.

5. *By increasing the volume of blood.*—During collapse and shock, specially from haemorrhage, the pressure diminishes which can be raised by (*a*) *transfusion of blood*; and (*b*) *injection of normal saline.* But since saline infusion has a tendency to diffuse into the tissues, the excess of fluid is readily excreted by the kidneys. A more permanent increase of blood volume is obtained by adding some colloid in the transfused fluid, as injection of gum saline (*see page* 88).

6. *Acting by stimulating the heart or increasing its output.*—See Cardiac Stimulants, page 282.

B. Drugs or measures which lower the blood pressure

1. *Acting by depressing the vaso-motor centre.*—Alcohol, chloral hydrate, ether, chloroform and narcotics depress the vaso-motor centre and cause a fall of pressure. They cause the vessels of the skin to dilate with consequent loss of heat. Coal tar antipyretics also produce the same effect. Surgical shock which occurs immediately after an injury is followed by a fall of blood pressure which has been attributed to exhaustion of the vaso-motor centre and which does not respond to normal afferent stimulation.

2. *Acting on the arterial muscle.*—These drugs when used subcutaneously, or taken by the mouth, or some of them when inhaled,

dilate arterioles and cause a fall of pressure. Certain products of metabolism also cause vaso-dilatation, as happens with slight increase of acidity of blood. Drugs belonging to this group are amyl nitrite and other nitrites, organic nitrates, carbachol, acetylcholine, theobromine.

3. *Acting by diminishing the volume of blood.*—This may be done by bleeding, venesection or by application of leeches. The volume of circulating blood may be reduced by diminishing the plasma. Thus purgatives and diaphoretics by withdrawal of fluids from the body reduce plasma volume.

4. *Acting by causing capillary paralysis.*—Histamine has a special toxic effect on the capillaries which are dilated causing a fall of pressure although the arterioles are constricted. By producing abnormal permeability of the capillaries it helps plasma to pass from blood to the tissues. Arsenic and antimony in poisonous doses possess a specific action on the capillaries and cause dilatation of the capillaries of the mucosa of the alimentary canal. Secondary shock also causes a fall of blood pressure and is supposed to be due to the production by the tissues of some substance having action similar to histamine.

5. *Acting by depressing the heart.* *See* Cardiac Depressants, page 299.

C. Drugs or measures acting locally on the vessels

1. *Local vascular stimulants*, or remedies which dilate arterioles when locally applied to the skin. They are alcohol, iodine, ammonia, tartar emetic, arsenious acid, camphor, cantharidin, capsicum, phenol, creosote, croton oil, chloroform, ether, mustard, volatile oils, hot applications, etc.

2. *Local astringents, haemostatics or styptics* are drugs which constrict the vessels when locally applied. They also cause shrinkage of the mucous surface. Those acting by contracting the muscular fibres are adrenaline, cold from any means, as evaporation of ether, ethyl chloride, or by application of ice. Vegetable astringents, and alum, silver, lead, iron, etc., act by coagulating the proteins in the tissues surrounding the vessels ; they have no action on the muscular coat of the vessel walls. Snake venom (Russell's viper) coagulates the blood and stops bleeding when locally applied.

Since local astringents are precipitated by proteins they cannot be absorbed nor can they exist in the blood and tissues in an effective form. It therefore stands to reason that these drugs cannot have any remote action and cannot stop bleeding when used internally except on the part where it directly comes in contact.

Remote haemostatics are drugs which when given internally by the mouth, or by injection, stop internal haemorrhage by helping coagulation of the blood. These are used mostly in haemophilia, haemoptysis and other forms of internal haemorrhages. They are calcium, congo red, haemostatic serum, vitamin K, etc.

Some drugs when used internally constrict the vessels after absorption. They are chiefly adrenaline, posterior pituitary, digitalis, ergot, etc. These are rarely used for the purpose of stopping haemorrhage, except ergot and pituitary extract in cases of uterine haemorrhage.

Vaso-constrictors are drugs which cause constriction of vessels by acting peripherally. They may act by stimulating the arterioles having a constrictor supply, or by acting directly on the muscles of the vessels, or by contracting the capillaries. They are adrenaline, ephedrine, tyramine, pituitary extract, ergotoxine, barium.

1. Drugs Raising the Blood Pressure

(a) Vaso-constrictors

ADRENALINA

Adrenaline. (Adrenal.)

Syn.—Epinephrine : Suprarenin ; Adnephrine.

Source.—It is *l-a-3*: 4-dihydroxyphenyl-ß methylaminoethanol. An active principle of the suprarenal gland. Obtained from an acid extract of the glands of certain mammals, or by synthesis.

Characters. A colourless or pale buff-coloured, sphaero-crystalline powder. Sparingly soluble in water ; *insoluble* in alcohol (90 p. c.) and in solvent ether. Soluble in aqueous solutions of mineral acids, and of sodium and potassium hydroxides. Not stable in neutral or alkaline solution, which becomes red on exposure to air. Natural adrenaline is laevorotatory.

B. P. Dose.—1/600 to 1/120 gr. or 0.1 to 0.5 mg. subcutaneously.

Enters into.—inj. Procain. et Adrenalin. Fort. and Mit.

OFFICIAL PREPARATIONS

1. **Liquor Adrenalinae Hydrochloridi.** *Syn.—Epinephrine Hydrochloride Solution.*—1 in 1000. To be kept in amber-coloured glass bottles.
2. **Injectio Adrenalinae. B. P. Dose.** By subcutaneous injection :—**2 to 8 ms. or 0.12 to 0.5 mil.**

NON-OFFICIAL PREPARATIONS

1. **Collyrium Adrenalinae Co., B.P.C.** *Syn.—Arc Eye Lotion.*—Contains boric acid 8 gr., zinc sulphate 1/2 gr., adrenaline hydrochloride solution 10 ms., fresh boiled and cooled distilled water, q.s. 1 oz.
2. **Nebula Adrenalinae, B.P.C.** *Syn.—Adrenaline Spray.* Solution of adrenaline hydrochlor. 1 oz. 20 ms., sod. chlor. 40 gr., sod. metabisulphite 5 gr., freshly boiled and cooled distilled water, q.s. 10 oz.
3. **Suppositorium Adrenalinae, B.P.C.**—Adrenaline 1/60 gr., boric acid 1/30 gr., water 1 min., wool fat 1½ gr., oil of theobroma, q.s. to form 15 gr.

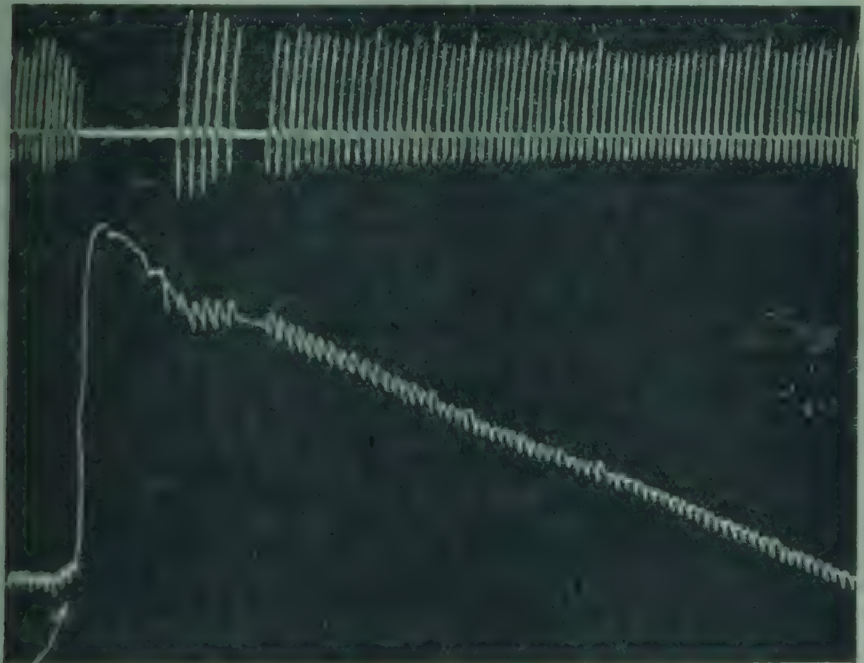


Fig. 17.—Anaesthetised Dog. Vagi intact.

Action of Adrenaline on Respiration and Blood Pressure. At point of arrow [illegible] solution of adrenaline was introduced into the femoral vein. Note the sudden rise of blood pressure. Respiration is inhibited at first (adrenaline apnoea) and gradually returns to normal. This effect is reflex from rise of blood pressure and not to respiratory depression.

PHARMACOLOGY

The main action of adrenaline is stimulation of the sympathetic nerve-endings, both motor and inhibitory, except those of the sweat glands. It does not act on the anatomical sympathetic nerve-endings and will produce its effects after the degeneration of the endings. It thus acts on some points between the nerve-endings and the tissue cells, i.e. at the point where the chemical transmitter is liberated by sympathetic nerve impulses. It therefore produces effects on all the organs of the body innervated by adrenergic nerves. Thyroid and adrenaline work together and the activity of the thyroid depends upon adrenaline, and conversely thyroid secretion sensitises tissues to the action of adrenaline. Cocaine and ephedrine potentiate the effect of adrenaline (*see* page 269 and 313).

Applied locally to mucous surface adrenaline causes blanching by powerfully **constricting the capillaries** and the **arterioles** at the site of application due to stimulation of the vaso-constrictor nerve-endings.

Eye.—Solution of adrenaline dropped into the eye causes the conjunctiva to become pale and shrunken, the eyelids retracted and makes the eye-ball appear more prominent. Given intravenously it causes dilatation of the pupil by stimulation of the sympathetic nerve-endings.

Heart and circulation.—Injected intravenously it

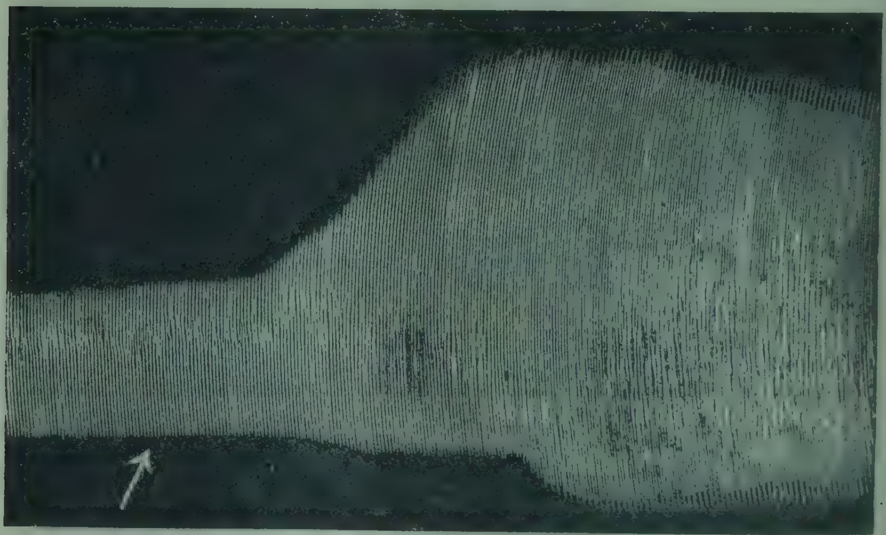


Fig. 18.—Record of the movements of an isolated Rabbit's Heart perfused with Ringer-locke solution showing effect of adrenaline. Note the great acceleration and increased force of beat.

causes a **rise of arterial blood pressure.** The pressure rises sharply and as it reaches the maximum the heart beats are strengthened and slowed. If the vagi are intact, as in normal animal, the rise is much less marked and is ac-

companied by definite slowing of the heart. Since the drug is quickly destroyed in the tissues by the enzyme amine oxidase, the pressure is not sustained and returns to normal quickly. If a second injection is given when the pressure is already high it sometimes causes a fall instead of the usual rise. If the sympathetic myoneural junction is paralysed by the previous use of ergotoxine an injection of adrenaline causes a distinct fall of pressure (vaso-motor reversal, *see* Ergotoxine). The rise of pressure is due to **constriction** of **arterioles** from the direct action of the drug on the myoneural junctions in the muscular coat of the vessel walls and cardiac stimulation. The intensity of its action depends upon the relative preponderance of the sympathetic innervation and in the intact animal the main constrictor effect falls on the richly supplied splanchnic area (except the intestinal vessels which usually dilate), the skin and the kidneys, and the minimum on the pulmonary and cerebral vessels. The coronary vessels are usually dilated, but very small concentrations cause constriction and diminish the flow of blood to the heart. It will thus appear that adrenaline does not cause general vascular constriction, while certain vessels, e.g. coronaries, intestinal and probably the skeletal muscles, are dilated even by relatively large doses, other vessels, e.g. of the skin, splanchnic viscera, except the intestinal ones, are constricted by any effective dose.

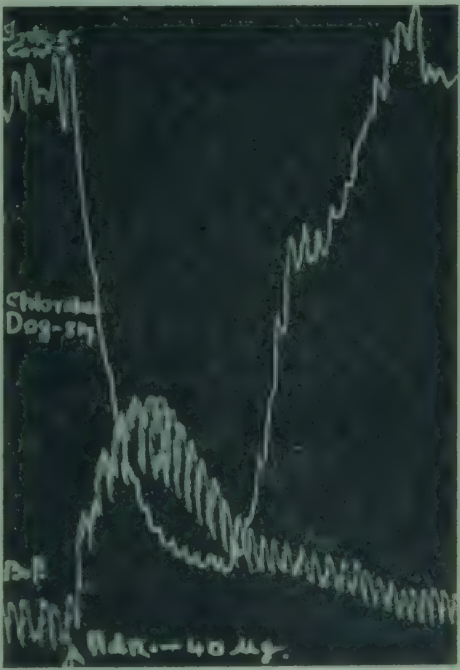


Fig. 19.—Dog under chloralose anaesthesia. Showing effects of adrenaline on blood pressure and intestinal contractions. Note—profound relaxation of the intestine along with rise of pressure.

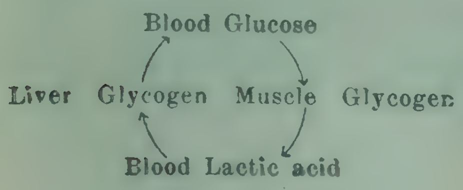
The **heart** is accelerated at first, then becomes slow, and finally becomes accelerated again. The quickening is the result of stimulation of the sympathetic endings in the heart muscle and is accompanied by more powerful contraction and complete emptying of the cavities. The slowing is a reflex effect caused by the rise of blood pressure which stimulates the afferent nerve-endings in the aortic arch and sinus caro-

ticus and is not produced after cutting the vagi or denervation of the sinus caroticus. As the coronary vessels are dilated, the heart muscle gets more nutrition and the tone is improved, while its oxygen metabolism is also increased in proportion to its activity and rate. It has however the drawback of favouring the occurrence of fibrillation, specially when used in chloroform and cyclopropane anaesthesia. In fact toxic doses produce auricular and ventricular fibrillation.

Respiration.—During the height of blood pressure following an injection, respiratory movements often cease or become shallow. This *adrenaline apnoea* (see fig. 17) is due to the same reflex which causes slowing of the pulse rate, *i. e.* rise of blood pressure. In small doses, used hypodermically, it causes increased depth of respiration and relaxation of the bronchial muscles by stimulation of the broncho-dilator (sympathetic) nerve endings.

Alimentary canal.—Given by the mouth adrenaline produces no systemic effect, possibly by constricting the arteries it prevents its own absorption. The slow absorption helps the destruction of the drug in the stomach before it reaches the circulation. Although it is rapidly destroyed some hold that if retained in the mouth it is sufficiently absorbed by the sublingual tissues to produce its systemic effects, chiefly rise of blood pressure and dilatation of the bronchial muscles. This however is doubtful. Secretion of saliva is increased and corresponds in character with that due to stimulation of the cervical sympathetic. After an intravenous injection adrenaline stimulates the ends of the splanchnics (sympathetic nerves to the alimentary canal) and lessens peristalsis of the stomach and intestine, but increases the contractions of the pyloric, ileocaecal and internal anal sphincters which receive the augmentor fibres from the sympathetic. The movements of the gall-bladder are inhibited but those of the bile-duct are stimulated.

Metabolism.—Adrenaline raises the basal metabolism within a short time after administration of 0.5 mil of 1 in 1000 solution. It increases the oxygen consumption by 20 to 40 p.c. and CO_2 production by from 30 to 50 p.c., thus raising the respiratory quotient.



The Cori Cycle

It produces glycogenolysis in the liver and in the skeletal muscles and therefore produces hyperglycaemia and glycosuria, i.e. it is antagonistic to insulin. When administered to animals after a prolonged fast it causes an increase in

liver glycogen due to breakdown of muscle glycogen to lactic acid, which is carried into the liver to be re-synthesised into glycogen. If the use of adrenaline is continued the liver glycogen is again converted into glucose which passes into the blood causing hyperglycaemia to be subsequently re-converted into glycogen in the muscle (Cori cycle).

Uterus.—Adrenaline causes contraction of the uterine vessels and of the uterus itself when pregnant. The effect varies with the different species of animals and in the same species, whether pregnant or virgin and depends upon the relative preponderance of the nerves whether motor or inhibitory. It usually relaxes the non-pregnant uterus of cat, but causes contraction during pregnancy. Surviving human uterus is stimulated whether pregnant or not (Lieb, 1915). It relaxes the force of contractions of the human pregnant uterus, specially during labour.

Muscle.—Adrenaline antagonises the onset of fatigue in skeletal muscles, and also increases the excitability and contractility of unfatigued muscle. Another striking effect of adrenaline is its anti-curari action which it develops more slowly though not so marked as that of potassium.

Urine and sweat.—The vessels of the kidneys are constricted even in doses too small to influence the general blood pressure and the secretion of urine is diminished but with the rise of pressure and subsequent relaxation of the renal vessels there is profuse **diuresis,** which continues for a little while even after the fall of the pressure. Urine often contains sugar due to an excess of sugar in the blood. Sweat glands though supplied by the sympathetic are not affected by it as the fibres are cholinergic (*see* page 231).

Toxic action.—(*a*) *Major symptoms.*—Acute dilatation of the heart with pulmonary oedema, ventricular fibrillation and death. These usually follow intravenous injection if the heart is already weak and diseased.

(*b*) *Minor symptoms.*—Palpitation, tachycardia, dyspnoea, rapid pulse, rise of blood pressure, muscular tremors, nausea, vomiting, vertigo and cold sweats.

Therapeutics of Adrenaline

Locally.—As a **haemostatic** adrenaline is largely used to stop all kinds of bleeding where it can be directly applied. It is specially valuable in capillary oozing or bleeding from minute vessels. For this purpose the liquor is either painted, or the part may be plugged with gauze soaked in it. It is used to stop bleeding from the nose, gums, or piles. For epistaxis it may be applied either as a nasal douche, or the posterior nares may be packed with gauze soaked in 1 in 1000 solution. For bleeding and inflamed piles it is applied either as a suppository or ointment. For its constricting effect it is used as a nasal

spray mixed with light liquid paraffin in hay fever, nasal catarrh and inflammation of the nose or throat.

Adrenaline is often combined with cocaine, procaine and other local anaesthetics to prolong their effect and also to reduce the chance of bleeding and toxicity by retarding absorption. The usual concentration necessary is $\frac{1}{2}$ to 1 minim of the liquor in 20 minims of the solution (*see* page 273).

Internally.—The chief use of adrenaline is as a **circulatory stimulant** in collapse and shock. Its action being of very short duration, it is suitable only in *emergency practice* and is not employed in ordinary conditions of failure of compensation. It may be added to saline infusion where there is considerable loss of fluid, as in the treatment of cholera. Two or 3 drops of the injection added to quinine solution when administered intravenously will prevent too great fall of blood pressure. In sudden stoppage of the heart in healthy persons, as for instance, in drowning and carbon monoxide poisoning, adrenaline injected directly into the heart may induce the heart to recommence beating, specially when accompanied with cardiac massage and artificial respiration. The intracardial injection should be given directly into the right ventricle, with a long fine needle, through the fourth intercostal space close to the sternum. Since chloroform increases the output of adrenaline, it should not be used in cardiac failure associated with chloroform anaesthesia as it may precipitate fibrillation of the heart.

It is occasionally of great value in complete **heart block** with extreme slowing of the ventricular rate.

There is no satisfactory evidence that adrenaline is absorbed by the alimentary tract. This limits its use for oral administration to oesophageal spasm, gastrostaxis and vomiting, when it acts locally on the appropriate sympathetic endings. It is also given to stop hiccough. The liquor (5 to 10 ms.) diluted with water will stop gastric haemorrhage.

As it relaxes the bronchioles it is especially valuable in **spasmodic asthma** when given hypodermically in 5 to 8 ms. doses of the injection. It may be combined with $\frac{1}{100}$ gr. of atropine or $\frac{1}{4}$ gr. of ephedrine hydrochloride when the latter drug acts as a synergist and prolongs the effect by preventing the action of amine oxidase. Small doses (1 to 3 ms.) are generally sufficient to abort an attack and produce no unpleasant symptoms which may follow injection of large doses given too rapidly. It is also used in urticaria, angioneurotic oedema, anaphylactic shock following serum injection, hypoglycaemia following the use of insulin, and to prevent the occurrence of **nitritoid reaction** which may appear after the use of organic arsenicals.

Caution.—1. It should not be used at all, or used with

caution in arteriosclerosis where there is risk of sudden rise of blood pressure.

2. In pulmonary or cerebral haemorrhage there is risk of increasing the haemorrhage.

3. In pulmonary oedema there is risk of increasing the oedema.

4. In cardiac failure from chloroform for fear of producing fibrillation.

5. It should be used with great caution to persons suffering from coronary arteriosclerosis and hyperthyroidism, and who are subject to attacks of cardiac pain and dyspnoea.

Mode of administration.—(*a*) *By mouth.*—For local action in the mouth and stomach. It is rapidly destroyed before it can enter the general circulation. Sometimes sublingual administration is resorted to for the production of systemic effects.

(*b*) *Subcutaneously*, when there may be a slight rise in blood pressure, but a marked-effect on the contracted bronchi; but owing to intense local vaso-constriction, it is very sparingly absorbed and a very small dose may not produce any systemic effect. Sometimes severe palpitation and muscular tremor may follow its use.

(*c*) *Intramuscularly*, causes rise in arterial pressure and relaxation of the bronchi.

(*d*) *Intravenously*, causes immediate and marked rise in arterial pressure. The best method in collapse and shock. The intravenous dose should be about 1/50th of the hypodermic dose and should be given very slowly and freely diluted.

(*e*) *Intracardially*, in sudden failure of the heart (4 to 10 ms.).

Noradrenaline. *Syn.*—Norepinephrine; Arterenol.—It is an immediate precursor of adrenaline from which it differs by the absence of an N-methyl group. Its action is entirely vasoconstrictor with little effect on the cardiac output. It has a more powerful effect on the uterus of pregnant cat. All other actions are weaker than adrenaline (see page 232).

SYMPATHOMIMETIC DRUGS

These are drugs with adrenaline-like action, having effect on the adrenergic nerves. Adrenaline is the only drug which has a true sympathomimetic action, *i.e.* produces the same effect on the different organs as will follow stimulation of the sympathetic nerves.

The following drugs are usually classed as having sympathomimetic action, *viz.* Ephedrine, Amphetamine (Benzedrine), Isoprenaline, Cobefrin, Neosynephrin, Propadrine, Pholedrine (Veritol), Methedrine, Tyramine and Paredrine. It will be seen that ephedrine differs from adrenaline in some important respects. It depresses the heart and stimulates the central nervous system. Cobefrin has a greater pressor effect and propadrine the least. As an aid to local anaesthesia cobefrin is five times and neosynephrin twenty times more powerful than adrenaline. Cobefrin is combined with procaine which is used for pro-

duction of local anaesthesia. None of these are as powerful as adrenaline in relaxing the bronchial muscle, nor have they any advantage as mydriatics, while they relax gastric and intestinal muscle in such doses as to affect the circulation. Neosynephrin causes constriction of the vessels and rise of blood pressure and when inhaled causes local vaso-constriction by acting directly on the muscles of the vessels like amphetamine (benzedrine), but does not stimulate the higher portions of the central nervous system like amphetamine. Pholedrine (veritol) causes prolonged vaso-constriction without accelerating the heart or producing cerebral excitement. It is therefore recommended in shock and vaso-motor paralysis. It resembles adrenaline in having low toxicity and having low toxic effect on the heart, and resembles ephedrine in its prolonged action after oral administration. Propadrine like ephedrine can be administered by the mouth and also possesses prolonged action, but does not give rise to anxiety reflex. It is chiefly used in allergic conditions.

The absorption of these drugs varies, depending upon their vaso-constrictor effect and chemical constitution. Those that are powerfully vaso-constrictor are absorbed less, and those that are chemically unstable are destroyed by the digestive juices. Therefore oral administration can be effective only if the drug is chemically stable and not too vaso-constrictive.

Ephedrine, amphetamine (benzedrine) and propadrine, without OH attached to the benzene ring resist decomposition and are found in the urine ; whereas adrenaline, cobefrin and neosynephrin with a catechol or phenolic nucleus are inactive when given by the mouth, in fact they are mostly destroyed in the body by whatever channel they are administered.

The **toxicity** of the drugs varies and depends upon (a) production of excessive hypertension, with consequent cardiac complication ; and (b) stimulant effect on the central nervous system, producing nervousness, excitement, tremors and insomnia. For the first effect, adrenaline is notorious ; and for the nervous effects, amphetamine (benzedrine) is most toxic, ephedrine comes next, and adrenaline and cobefrin last. Others do not produce any nervous effect in therapeutic doses.

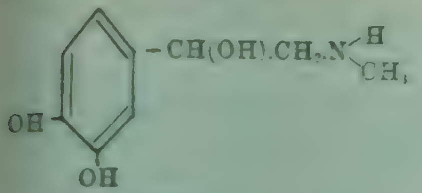
EPHEDRINA

(Ephed.)

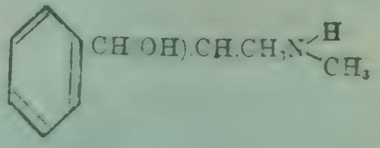
Source.—Ephedrine is the hemihydrate of *l*-*a*-hydroxy-*β*-methylaminopropylbenzene, an alkaloid obtained from *Ephedra sinica*, *E. equisetina*, and other species of *Ephedra*, or prepared by synthesis.

Characters.—In colourless, non-deliquescent, non-efflorescent, hexagonal, prismatic crystals ; odourless, or has acquired a slight unpleasant smell. Readily

soluble in water, in alcohol (95 p.c.), in solvent ether, in chloroform. Soluble in about 20 parts of glycerin, 25 parts of olive oil, and in about 100 parts of liquid paraffin, with separation of water, only the anhydrous alkaloid forming a clear solution in that solvent.



Adrenaline



Ephedrine

Ephedrinae Hydrochloridum. (Ephed. Hydrochlor.).—Ephedrine Hydrochloride is the hydrochloride of the alkaloid, ephedrine.

Characters. Colourless crystals; odourless; taste, bitter. *Soluble* in water and alcohol (90 p.c.). Aqueous solution neutral to litmus.

B. P. Dose.—1/4 to 1 gr. or 16 to 60 mg.

Official Preparation

1. **Tabellae Ephedrinae Hydrochloridi.—B. P. Dose.—1/4 to 1 gr. or 16 to 60 mg.** If the quantity to be contained in a tablet is not stated, 1/2 gr. tablet shall be supplied.

Non-official Preparations

1. **Extractum Ephedrae Liquidum, I. P. L.**—Ephedra 1000 G., alcohol (90 p.c.) q.s. to contain 2 p.c. ephedrine. *Dose.*—20 to 30 ms. or 1.5 to 2 mils.
2. **Tinctura Ephedrae, I. P. L.**—Liquid extract of ephedra 250 G. alcohol (40 p.c.) 1000 mils. Contains 0.5 p.c. ephedrine. *Dose.*—90 to 120 ms. or 6 to 8 mils.
3. **Elixir Ephedrinae Hydrochloridi, B.P.C.**—Contains 1/4 gr. ephedrine hydrochloride in 60 ms. *Dose.*—1/2 to 2 drs. or 2 to 8 mils.
4. **Nebula Ephedrinae Aquosa, B.P.C.** Ephedrine hydrochlor. 4 gr., sod. chlor. 2 gr., chlorbutol 2 gr., water, q.s. 1 oz.

Pharmacology

Ephedrine is closely related to adrenaline and tyramine. Its molecule differs from adrenaline by the absence of the two hydroxyl groups and the presence of an extra methyl group. These make it more stable. Its action resembles adrenaline, the effects being produced from stimulation of the sympathetic nerve-endings. In large doses it has various other effects, which have been ascribed to an indiscriminate stimulation of smooth muscle and to stimulation of the autonomic nerve ganglia.

It stimulates the central nervous system like amphetamine and large doses produce insomnia, tremors and anxiety reflex specially in women. It does not reduce the secretions, and some observers claim that it stimulates the intestinal muscles which are depressed by adrenaline. Our observation is that its effect on the gut muscle is the same as adrenaline, *i.e.* relaxes the muscle (*see* fig. 20). Owing to rise of blood pressure the amount of urine is increased. The uterus contracts in all animals, but is less sensitive to this drug than adrenaline.

Just as eserine acts by inhibiting the action of choline esterase and prolongs the action of acetylcholine, ephedrine increases the action of adrenaline in much the same way by inhibiting the action of amine oxidase. *

* Gaddum, *British Medical Journal*, April, 2, 1938.

Locally applied to denuded surface or mucous membrane ephedrine causes vaso-constriction. It is not absorbed by the unbroken skin.

Eye.—A solution of ephedrine dropped into the eye or used internally causes slight mydriasis without affecting accommodation or increasing the intra-ocular tension and producing little effect on the conjunctival vessels. All these effects are due to stimulation of the sympathetic myoneural junction, and are elicited, by 1 to 5 p.c. solution.

Internally.—Ephedrine is absorbed from mucous surfaces, stomach and rectum. The absorption however is slow and the effects last longer than adrenaline. It is a more stable compound, due to the fact that ephedrine is immune to enzyme amine oxidase, which normally destroys adrenaline, and its solution can be sterilised by boiling.

Heart and circulation.—Administered by the mouth or hypodermically it stimulates the myoneural junctions of the sympathetic in the heart and the vaso-constrictors, but less powerfully than adrenaline, causing **acceleration of the heart, and rise of blood pressure,** which is more prolonged. The duration is increased 7 to 10 times than that produced by adrenaline. This pressor effect is not reversed by the previous use of ergotoxine or ergotamine. The heart rate becomes slow with the rise of pressure. The rise of blood pressure is not proportional to the dose and

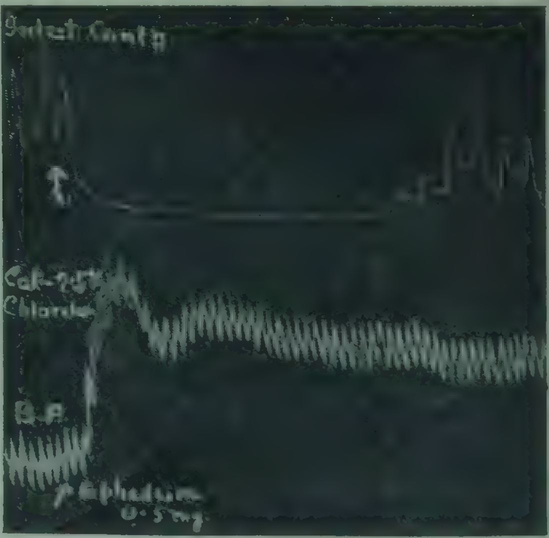


Fig. 20.—Cat under chloralose. Showing effect of ephedrine on intestinal movements and blood pressure. Note—prolonged rise of blood pressure and relaxation of intestinal movements. The intestinal effect passes off earlier than that of the blood pressure, c.f. adrenaline (fig. 19).

becomes less with successive doses, exhibiting the phenomenon of tachyphylaxis, not observed with adrenaline. It does not stimulate the heart directly but the effect is indirect through its action on the cardiac accelerator nerve. In large doses the heart is depressed.

Pseudo-ephedrine has action similar to ephedrine but weaker, it is however a direct stimulant to the heart.

It increases the red cells and leucocytes due possibly to extrusion into the circulation of erythrocytes, leucocytes and platelets from the storage and haemopoietic centres including the bone marrow.*

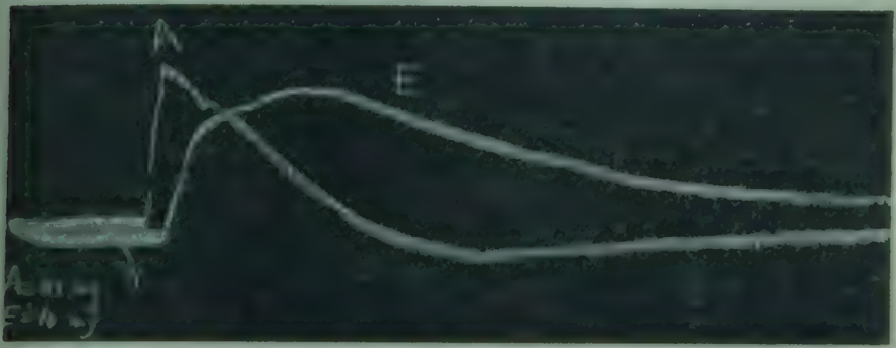


Fig. 21.—Anaesthetized cat. A. adrenaline ; E. ephedrine. Showing effects of adrenaline and ephedrine on blood pressure in contrast.

Respiration.—Ephedrine **stimulates the respiratory centre**, and relaxes the bronchial muscles specially when constricted as in asthma, or after physostigmine. This effect is produced by its action on the broncho-dilator (sympathetic).

Clearance.—Ephedrine is excreted in the urine unconjugated and unchanged. Both ephedrine and amphetamine are inactivated in the body by certain enzyme system (ascorbic acid-dehydroascorbic acid) which is known to deaminate certain amino acids. Moreover excretion of ephedrine is diminished when large doses of ascorbic acid is given simultaneously.

Therapeutics

Ephedrine is used in the same conditions where adrenaline is indicated. In **bronchial asthma** the hydrochloride gives relief within 20 to 30 minutes when administered by the mouth in $\frac{1}{4}$ to $\frac{1}{2}$ gr. doses, and given two to three times a day it will keep away the attacks. It is not so potent as adrenaline in severe attacks, and very soon toleration is induced, and a larger dose is required to produce the same result. Some patients complain of severe sweating and sleeplessness, while others show no effect after a single dose of $\frac{1}{2}$ gr. Since ephedrine potentiates the action of adrenaline, it is often combined with it when the effect lasts for a longer time. It relieves **whooping cough**, specially during the second stage, when given in $\frac{1}{8}$ or $\frac{1}{4}$ gr. doses twice a day to children one year old.

It is used in anaphylactic shock, hay fever, urticaria

*Simpson and Cadness ; *Journal of Pharmacology*. 1936

and in angio-neurotic oedema, and as an addition to loca anaesthetics in place of adrenaline. It counteracts th collapse which follows the use of spinal anaesthesia. In hay fever it acts both when given by the mouth and as a nasal spray (3 to 5 p. c.), when it causes shrinkage of the engorged mucous membrane. This effect has been foun useful in the treatment of cold and has been utilised in nasal surgery.

In narcotic poisoning it not only stimulates the respira tory and vaso-motor centres but also exerts an analepti action on higher cerebral centres and thus lessens the degree of depression.

Since ephedrine increases the tone of skeletal muscles it is used in **myasthenia gravis** when ¾ gr. daily cause progressive increase in strength by the retention of crea tine in the muscle and by virtue of its anti-curari effect It lessens the tremor and weakness in post-encephaliti parkinsonism.

Because of its stimulating effect on the central ner vous system it may be used to prevent pathological slee in **narcolepsy**, a condition characterised by drowsines when inactive.

By improving the tone of the sphincter of the bladde it improves **nocturnal incontinence of urine** in childre when given in ½ gr. doses at bed-time to a child 10 to 1 years old.

Its use has been recommended in complete **heart-bloc** and Gilchrist * used it in ½ gr. doses in this condition wit Stokes-Adams' syndrome three times a day. It relieve nerve pain in leprosy better than injections of adrenaline

As it contains some pseudo-ephedrine, the tincture i used as a **stimulant** to the heart in pneumonia, astheni conditions, low blood pressure, etc.

Caution.—It should be used with caution in patients with or anic heart disease or cardiac decompensation, hyperthyroidism, thos suffering from high blood pressure or angina pectoris.

Toxic symptoms.—Large doses cause tachycardia, tremor vertigo, palpitation, sweating, nausea and irritation of the bladde with difficulty in passing urine and faeces. They are associate with high blood pressure and disappear when it returns to norma The chief danger is cardiac depression and it should not be used i cardiac asthma, when the heart is damaged, and in acute circulator collapse.

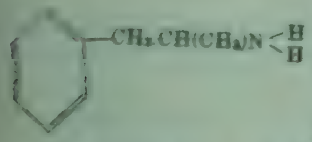
Some patients are specially sensitive to ephedrine and even small single dose (1/2 gr.) given for the relief of asthma or urtic ria produces symptoms of collapse, perspiration, tremor, palpitatio etc. It causes euphoria in some people.

Ephetonin. (*Not official*). *Syn.—Synthetic Ephedrine.*—A hy drochloride of *phenylmethylaminopropanol.* Closely related to eph drine and has properties similar to ephedrine or adrenaline. Give orally in the same conditions where adrenaline is indicated. Supplie

* *British Meidcal Journal*, April 7, 1934.

in tablets of 3/4 gr. (50 mg.) each and in ampoules for hypodermic injection.

AMPHETAMINA. (Amphetamin.). **Syn.**—Benzedrine.—Amphetamine is β-aminopropylbenzene and may be prepared by the reduction of the oxime of phenylacetone. Contains not less than 97.0 p.c. of $C_9H_{13}N$.



Characters.—A colourless, mobile liquid ; odour, slight and characteristic ; taste, acrid ; volatilises slowly at ordinary temperatures.

Amphetaminae Sulphas. (Amphetamin. Sulph.). *Syn.*—Benzedrine Sulphate.—Amphetamine Sulphate is ß-aminopropylbenzene sulphate.

Characters.—A white, odourless powder ; taste, slightly bitter, followed by a sensation of numbness. *Soluble* in 8.8 parts of water and in 515 parts of alcohol (90 p.c.) ; insoluble in solvent ether.

B. P. Dose.—1/24 to 1/6 gr. or 2.5 to 10 mg.

Pharmacology and Therapeutics

Amphetamine is closely allied to ephedrine in chemical structure but differs in that ephedrine has a hydroxy group on the alpha carbon and methyl group on the amino nitrogen. It differs from adrenaline in its effectiveness after oral use, a prolonged duration of action, marked central stimulating effect, the analeptic action being related chiefly to the three carbon chain with the amino group attached to the middle carbon and the absence of OH groups on the benzene ring.

The action of amphetamine resembles adrenaline or ephedrine when applied locally. Being volatile, when inhaled, it causes local vaso-constriction and shrinkage of the mucous membrane, and is used in acute coryza, hay fever, and all catarrhal conditions of the respiratory tract. It is available in the form of inhaler, consisting of benzedrine 0.325 grm. with oil of lavender and menthol.

The sulphate is not volatile and therefore can be taken by the mouth. Its action resembles adrenaline or ephedrine and is a stimulant to the sympathetic system. It raises the blood pressure without any effect on the pressure of spinal fluid, paralyses intestinal activity, and powerfully stimulates the higher portions of the central nervous system giving rise to increased energy and capacity for work, and a feeling of well-being. It may cause pronounced psychological effects which are characterised by increased confidence and initiative, ease in making decisions, and inclination to talk more than usual. There may be restlessness which may be pleasant or unpleasant. Some complain of dizziness, palpitation, headache, delirium, depression or fatigue. The reversal of central effect may follow continuous use of even of moderate doses. It causes an increase of red and white cells due possibly to contraction of the spleen.

Like ephedrine it stimulates the respiratory centre. This effect is more marked when there is central depression and is therefore of great value in **narcotic poisoning**. It relaxes the bronchial muscles.

The sulphate may be administered internally, and its use has been recommended in shock, fatigue, nervous exhaustion, and spasm of the involuntary muscles, as asthma, colic, etc. It is of value in **post-encephalitic parkinsonism,** specially when drowsiness and lack of energy predominate, and is more effective when combined with scopolamine or stramonium. It has also been recommended in alcoholism, drug addiction, primary dysmenorrhoea, and also certain types of "war neurosis."

It is largely used in mental disorders, for preventing **narcoleptic attacks,** and in various forms of **psychoneuroses** to prevent fatigue.

Amphetamine is being used in **obesity** on the idea that it might help to reduce weight indirectly by depressing appetite by producing cessation of stomach contraction normally responsible for the sensation of hunger. It is used in doses of 15 to 30 mg. ($\frac{1}{4}$ to $\frac{1}{2}$ gr.) daily in three divided doses, at morning, noon and evening, commencing with 2.5 mg. ($\frac{1}{24}$ gr.) and slowly increasing to 10 mg. ($\frac{1}{8}$ to $\frac{1}{2}$ gr.).

Dextrorotatory amphetamine (Dexedrine) has stronger central action and less effect on the peripheral nervous system and is used in the treatment of obesity in preference to amphetamine in doses of 5 mg. ($\frac{1}{12}$gr.) three times a day during the greatest hunger contractions. It should be used under careful medical supervision.

Contra-indications.—Arteriosclerosis, coronary artery disease, maniac excitement. Since prolonged inhalation may give rise to restlessness and insomnia, it should not be repeated too frequently, *i.e.* not within an hour. It should not be used in those suffering from high blood pressure.

Untoward symptoms.—These may be physical or psychological. Difficulty in passing urine and faeces, loss of weight, skin rash, rise and sometimes paradoxical fall of pressure, and transient heart-block.* Taken in excess for prolonged period it causes aplastic anaemia.

Methedrine. (Not official). **Syn.**—Pervitin; Desoxyephedrine.—It is d-N-Methylamphetamine hydrochloride. **Dose.**—1/20 to 1/10 gr. or 3 to 6 mg.

ACTION AND USES.—It is a **cerebral stimulant** like amphetamine and also causes vaso-constriction with rise of blood pressure. It increases mental and physical efficiency and is therefore used in narcolepsy, mental depression and coma. Because of its **analeptic** effect it is used in collapse from overdosage of anaesthetics or narcotics, e.g. in barbiturate and morphine poisoning. It can be administered subcutaneously, intramuscularly or intravenously to restore the blood pressure after major operations or after spinal anaesthesia. May be administered by the mouth for central stimulant effect.

* Davies, *British Medical Journal ; Sept.* 25, 1937.

Isoprenaline. (Not official). **Syn.**—Aleudrine; Neodrenal; Neo-epinine.—It is *iso*Propylnoradrenaline, shares with adrenaline and noradrenaline tendency to produce tachycardia but causes fall of pressure and is a better bronchodilator and well absorbed when given by the mouth, by inhalation, sublingually, or by injection. Chiefly used in cases of **asthma** when adrenaline has failed to give relief. As a *nasal spray* it is used in 1 in 200 solution. The *sublingual route* should be selected when inhalation cannot be carried out. A 10 mg. tablet allowed to dissolve under the tongue until relief is obtained or side-effects have appeared when it should be spat out.

Non-official Sympathomimetic Drugs

1. **Paredrine.**—*p*-Hydroxy-*a*-methyl-phenylethylamine hydrobromide. Has a powerful pressor action due to stimulation of the smooth muscle of the arterial wall and is effective when given by mouth, intramuscularly or intravenously. **Dose.**—20 or 30 mg. (1/3 or 1/2 gr.) *orally* ; 10 or 20 mg. (1/6 or 1/3 gr.) *intramuscularly* ; 5 or 10 mg. (1/12 or 1/6 gr.) *intravenously.*

2. **Tyramina.**—Tyramine is a base occurring in ergot ; also prepared synthetically. It resembles adrenaline in its action, but the effect is weaker and more prolonged. It has no local haemostatic action. Used in the treatment of shock and collapse, by injection of the solution of a soluble salt, in **doses** of 20 to 40 mg. (1/3 to 3/5 gr.).

3. **Pholedrine.** *Syn.*—*Veritol.* –β-(4-Hydroxyphenyl)-isopropylmethylamine. A circulatory stimulant and restorative, having a less rapid but more prolonged action than adrenaline, and without the cardiac of ephedrine. **Dose.**—(*As a circulatory tonic*) 10 to 20 drops or 1/4 to 1/2 tablet several times daily, or 1/2 ampoule intramuscularly or subcutaneously, or 1/4 ampouleintravenously. (*As a restorative in collapse*) 1/2 to 1 ampoule intravenously hourly if necessary or 1 ampoule intramuscularly or subcutaneously.

4. **Propadrine Hydrochloride.**—It is the hydrochloride of *dl*-phenyl-1-amino-2-propanol-1, a base resembling ephedrine. Freely soluble in water. Has an action similar to that of ephedrine but somewhat more prolonged. Employed internally in allergic manifestations. **Dose.**—3/8 to 3/4 gr. (24 to 50 mg.).

5. **Cobefrin.**—It is *o*-dioxyphenylpropanolamine, a synthetic vaso-constrictor, readily *soluble* in water, and exerts the vaso-constrictor action of adrenaline without its deleterious action on the circulation. A combination of novocaine and cobefrin, issued in tablets and solution of various strengths for local anaesthesia.

6. **Neosynephrin.**—It differs from adrenaline in having only one hydroxyl group attached to the benzene ring (meta-position) and from **Synephrin,** the older compound, where the OH group is in the para-position. Applied locally to mucous membranes in a 0.25 to 0.5 p. c. solution it constricts the smaller vessels and reduces congestion and swelling and it may be therefore used in rhinitis and hay fever. It is also used to prolong the anaesthesia produced by procaine, etc.

2. Drugs Lowering the Blood Pressure

Vaso-dilators

Vaso-dilators are drugs which dilate the arterioles and lower the blood pressure ; they act in the following ways :—

1. *Depressing the vaso-motor centre.*—Narcotics, chloroform and ether anaesthesia.
2. *Depressing the sympathetic nerve cells.*—Nicotine.
3. *Depressing the plain muscles of the vessels.*—Nitrites, carbachol, acetylcholine, papaverine, theobromine.
4. *Paralysing the capillaries.*—Histamine, arsenic and antimony in poisonous doses.
5. *Depressing the vaso-motor nerve endings.*—Ergotoxine in large doses. Apocodeine.

AMYLIS NITRIS

Amyl Nitrite. (Amyl. Nitris).

Source.—Contains not less than 90 p.c. of nitrites, calculated as $C_5H_{11}O_2N$. Consists chiefly of the nitrites of *iso*-butylcarbinol, and *sec.*-butylcarbinol, with other nitrites of the homologous series.

Characters.—A clear, yellow liquid ; odour, fragrant ; taste, pungent and aromatic ; very volatile. *Miscible* with alcohol (90 p.c.), and with solvent ether ; insoluble in water.

Dispensing hint.—It should be kept in hermetically sealed bottles in a cool, dark place. Agitation or heat helps evaporation.

B. P. Dose.—2 to 5 mins. or 0.12 to 0.3 mil by inhalation.

Pharmacology

Internally. **Blood.**—It enters the blood readily throug the lungs and stomach, and circulates as sodium nitrit If absorbed in large quantity, it converts the oxyhaemo globin into methaemoglobin and another body—nitri oxide haemoglobin—and renders the arterial and venou blood chocolate-coloured, and thereby interferes with th oxidising property of the corpuscles causing breathlessnes and cyanosis. In ordinary doses the effect is slight an the methaemoglobin is soon deoxidised, but in toxic dose these changes are enough to cause death. The inhalatio of oxygen soon reconverts methaemoglobin.

Heart and blood vessels.—Within a few seconds of in halation, the face, head and neck become warm and flushe the carotids and their branches throb, head feels full an tense, and the heart beats rapidly and violently, soon fo lowed by headache, giddiness, rapid breathing and dilata tion of the pupils. All these effects are due to dilatatio of the vessels of the head and neck (blush area). Bu very soon the vessels of the whole body dilate with enor mous fall of blood pressure. With inhalation of 3 to 5 m the fall may be about 15 to 20 mm. of mercury. Th vaso-dilatation is due to direct action of the nitrite on th

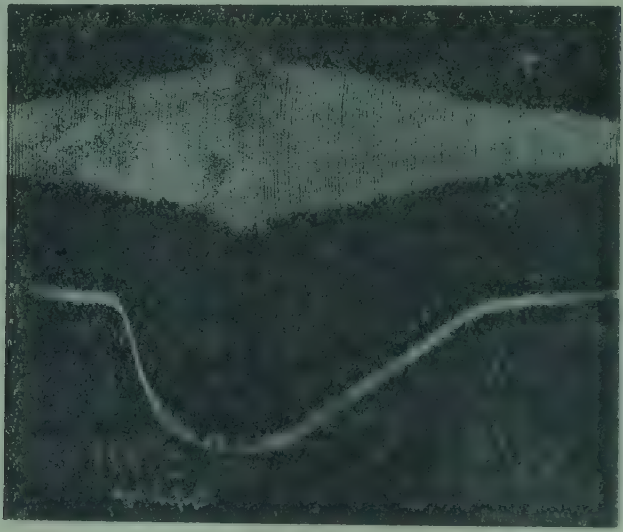


Fig. 22.—Dog. Respiration and Blood Pressure.

At point of arrow amyl nitrite was given by inhalation. Note—fall of blo pressure and stimulation of respiration which becomes quicker and deeper.

vessel walls and not to any effect on the vaso-motor centr The blood pressure does not fall if the nitrite is intro duced into the cerebral circulation and prevented fron reaching the peripheral vessels. On the other hand ther is vaso-dilatation after ligature of the vessels to the brain

after destruction of the spinal cord, and when applied to excised organs or arterial segments. The dilatation is more marked in the splanchnic area and the extremities. The coronary, pulmonary and cerebral vessels also dilate.

After inhalation there is at first slight slowing of the heart due to reflex vagus stimulation. Very soon however the rate quickens owing to the relaxation of the vagus control in the medulla and the amplitude of contractions is also increased in an effort to compensate for the reduced blood pressure. The heart muscle shows no important change, but the improved coronary circulation and lowered peripheral resistance may improve and relieve a weak heart. Large doses however depress the heart and make it weak and slow.

Muscles.—The activity of most of the involuntary muscles is depressed, but the effect on arterial muscles is most marked. The muscles of the bronchioles, uterus and intestine also become relaxed.

Lungs.—Respiration is at first quickened from stimulation of the respiratory centre through diminished supply of blood to the brain as a result of the fall of blood pressure. Later it becomes laboured and difficult, and finally ceases when the centre becomes asphyxiated.

Nervous system.—When inhaled for a short time and in small quantities it has very little effect on the higher parts of the central nervous system. But the medullary centres may be slightly stimulated at the beginning reflexly from irritation of the sensory terminations of the nasal mucous membrane. With the fall of blood pressure and consequent anaemia of the medulla the activity of the inhibitory centre of the heart is depressed and both the respiratory and vaso-motor centres are stimulated. Most of the nervous symptoms such as headache, giddiness, throbbing in the head, etc., are due to the dilatation of the arterioles and fall of blood pressure. The function of the sensory and motor nerve is affected before death.

Eye.—There is a temporary blurring of the sight as a result of the dilatation of the retinal vessels, dilatation of the pupil and increase of intra-ocular tension.

Clearance.—It escapes with the urine as nitrites and nitrates, but the quantity is less than what is absorbed, about 60 to 70 p.c. disappearing in the body.

THERAPEUTICS

Inhalation.—The chief use of amyl nitrite is in **angina pectoris**. Since anginal attacks may occur without a corresponding rise of blood pressure its action is possibly due to relaxation of the coronary spasm. Five drops give speedy relief, especially if the disease is paroxysmal. In fact, it relieves, though temporarily, any cardiac **pain** of a

paroxysmal nature, but its action is of such fleeting nature as to render it useful only in emergency and should be followed during the interval of attacks by sodium nitrite or nitroglycerin.

On account of its action in lowering blood pressure its use has been advocated in **haemoptysis** on the idea that it will help formation of clot at the point of injury, and in urgent cases it may be found to give good results.

It has been found efficacious in uncomplicated **asthma** relieving dyspnoea within a short time. It also temporarily affords relief to **cardiac dyspnoea** by lowering the pressure of the systemic arteries. It may relieve the pain of dysmenorrhoea and relax uterine spasms.

Caution.—It should be used with great caution in sensitive and nervous persons, who are powerfully affected by it. It should not be administered to persons suffering from aortic diseases, advanced degeneration of the cardiac muscle, those whose arteries are atheromatous, or to those who are emphysematous, plethoric or suffer from chronic bronchitis.

Prescribing **hints.**—Inhalation is the usual method. The drug may be poured on a handkerchief, or a glass capsule broken within its folds and inhaled. The glass capsules keep better in India. Patients may become habituated to its use, so that after a while it has to be inhaled several times before it will give relief.

Octyl Nitris, B.P.C.—Octyl nitrite is 2-ethyl-*n*-hexyl-1-nitrite. A clear yellow volatile liquid. Its action is similar to amyl nitrite but the effect is more prolonged and is used by inhalation. There is less chance of methaemoglobin formation and is used in the same conditions where amyl nitrite is indicated, e.g. anginal attacks, coronary spasms, and also in spasms of the cardiac sphincter of the stomach. Supplied like amyl nitrite in breakable glass capsules covered with cotton wool and silk.

Liquor Glycerylis Trinitratis. (Liq. Glyc. Trinit.). **B.P.C.** **Syn.**—Solution of Nitroglycerin ; Spiritus Glycerylis Nitratis ; Liquor Trinitrini.

Characters.—A clear, colourless liquid, neutral to litmus.
Dose.—1/2 to 2 ms. or 0.03 to 0.12 mil.

Official Preparation

1. **Tabellae Glycerylis Trinitratis.** *Syn.—Tabellae Trinitrini ; Nitroglycerin Tablets.*—**B. P. Dose.—1/130 to 1/60 gr. or 0.5 to 1 mg.**

Erythritylis Tetranitras Dilutus, B.P.C. (Erythrityl. Tetranit. **Dil.**). Syn.—Erythrol Tetranitrate (50 p.c.).

Diluted Erythrityl Tetranitrate is a mixture of approximately equal weights of erythrityl tetranitrate and lactose. Contains 47.5 **to 52.5 p.c. of $C_4H_6O_{12}N_4$.**

Characters.—A white powder ; odourless ; tasteless, except for the slight sweet taste of lactose. Partially *soluble* in water, and in alcohol (90 p.c.).

Dose.—1/2 to 2 grs. (30 to 120 mg.), representing 1/4 to 1 gr. (15 to 60 mg.) of pure erythrityl tetranitrate.

Pharmacology and Therapeutics

Nitroglycerin is absorbed unaltered by the stomach but on reaching the blood it is decomposed into glycerin, nitrites and nitrates. Its action is the same as that of

amyl nitrite but the effects, though not so prompt, are lasting. Administered under the tongue its absorption is more rapid than when swallowed. In fact sublingual administration is adopted for prompt effect and in preference to amyl nitrite in the treatment of **angina pectoris.** Generally nitroglycerin is given in the intervals of attacks every four to six hours to prevent further attacks, and amyl nitrite is reserved for administration during the actual onset of the paroxysm. One of the drawbacks to the use of this drug is that it is apt to cause a severe throbbing headache. Since nitroglycerin is not wholly broken up in the system it has been suggested that the headache is due to the undecomposed molecule and not to the nitrite constituent. Patients rapidly become habituated.

Although it has no direct action on the heart its use has been advocated in different forms of cardiac diseases, and the benefit which follows its use is indirect due to vascular dilatation which decreases the resistance against which the left side of the heart is working. On the other hand its use is contra-indicated in advanced heart disease where the heart muscles are degenerated. Here the blood pressure is already low and any further reduction of the pressure will not only lead to syncope from anaemia of the brain, but a low coronary pressure will also lessen the nutrition of the heart and still further weaken the muscle.

It is largely used for the purpose of lowering supernatural blood pressure, but the general experience of clinicians is that the drugs of this group often fail to produce any permanent lowering of pressure.

It is used in sea-sickness, chronic Bright's disease and various spasmodic disorders.

Erythrol tetranitrate has a more prolonged action than amyl nitrite or nitroglycerin, and being more slowly absorbed the fall of pressure begins in about 5 to 15 minutes and is maintained for about two hours.

SODII NITRIS. (Sod. Nitris). $NaNO_2$.—Sodium Nitrite may be obtained by reducing sodium nitrate with metallic lead. Contains not less than 95 p.c. of pure sodium nitrite.

Characters.—Colourless, or slightly yellow crystals, or a white, or slightly yellow granular powder. Taste, saline; odourless. Deliquescent. *Soluble* in 1.5 parts of water.

B. P. Dose.—1/2 to 2 grs. or 30 to 120 mg.

Pharmacology and Therapeutics

Sodium nitrite possesses properties similar to amyl nitrite and nitroglycerin, but it is slower in its action than the former and does not cause so much throbbing and headache as the latter. It is used in angina pectoris, aortic disease, and in the increased arterial tension which accompanies granular kidney. In the air it gradually oxidises to nitrate and loses its efficacy. Given during the digestive period, *i.e.* while there is free hydrochloric acid,

it sets free nitrous acid, which is not only irritating t the stomach but may be partly oxidised and rendered iner before absorption.

It has been used with success in hemicrania and i bronchial asthma. For asthma, it is given combined wit hyoscyamus in doses of 1 to 3 grs. frequently repeate Because nitrites form methaemoglobin, sodium nitrite i used in **cyanide poisoning** where methaemoglobin unite with cyanide ion to form cyanmethaemoglobin which i comparatively innocuous. It is used intravenously i 1 p.c. solution slowly. Commencing with 10 mils with total of 50 mils in one hour.

GROUP VIII

DRUGS ACTING ON THE RESPIRATORY SYSTEM

There is an intimate relation between the respirator organs, the external air, the blood, the circulation, th nervous system and the respiratory centre. A disturbanc in any one of them at once reflects upon the respirator mechanism. The chief function of respiration is to sup-ply oxygen to the tissues and to excrete CO_2 and thi oxygen requirement and CO_2 excretion are proportional t the degree of activity of the body. This gaseous exchang in the lungs and the tissues takes place according to th physical law of diffusion of gases, *i.e.* the gas diffuses fro a point of high tension to one of lower tension till equili-brium is established, when the diffusion becomes equal i both directions. Any failure of respiration is accompanie by deprivation of oxygen and accumulation of CO_2.

The complex process involved in respiratory move-ments is controlled by the *respiratory centre* situated i the pons and upper part of the medulla at the level of th calamus scriptorius. Although sensitive to various refle stimulation, the centre is autonomus. It is possible tha there are two centres, one normally concerned is the in-spiratory centre which co-ordinates the inspiratory muscle concerned in the respiratory movements ; the expiratio being purely passive, the centre for expiration is no brought into activity except under special circumstances. The impulses of both inspiration and expiration for th entire respiratory mechanism are distributed in a co-ordi-nated way to the lower motor centres in the cord, and i the case of nose and larynx to the motor centres of th vagus and facial.

The vagus is the chief nerve of respiration, containi both sensory and motor fibres and therefore plays a mo important part in respiratory functions. The afferent fila-ments which abundantly supply the wall of the air passa-ges and probably the lungs constantly transmit impress-ions to the centre and modify respiratory movements.

Again, the muscles of the bronchi being supplied with the efferent fibres of the vagus are constantly affected by various afferent impressions which may even arise in the air tubes themselves. Besides the vagus, afferent nerves passing from the carotid sinus and aortic arch are actively concerned with the regulation of breathing. The afferent fibres from the laryngeal mucous membrane are concerned with the cough reflex which guard the respiratory passages against the entrance of foreign bodies.

The respiration is also influenced by variations in the blood pressure. A rise in the pressure reflexly depresses respiration while a fall stimulates breathing. This effect is reflex, produced by the presso-receptors in the carotid sinus and aortic arch.

Apart from the nervous control, the centre is highly sensitive to the conditions of the gases in the body. If the blood becomes more venous, the centre is stimulated and the respiratory movements augmented both in rate and force. Conversely, if the blood is more oxygenated by free ventilation of the lungs, or the tension of CO_2 is diminished, the centre acts more feebly, or may fail to act giving rise to a condition known as *apnoea*. The centre therefore is stimulated when the CO_2 tension of plasma is increased. The CO_2 combines with water and forms carbonic acid, H_2CO_3, which dissociates to yield H-ion thus increasing the hydrogen-ion concentration of the blood which stimulates the centre. Respiration therefore is very sensitive to the slightest change in the hydrogen-ion concentration of the blood and responds in such a way as to keep the reaction at its normal level. Similarly after exercise a large amount of carbon dioxide is discharged into the plasma increasing its hydrogen-ion concentration which stimulates the respiratory centre resulting in augmented breathing, by which the excess of CO_2 is removed and more oxygen is absorbed to supply the muscles. Just as increased tension of carbon dioxide stimulates the centre so a lack of oxygen, though it does not directly stimulate the centre, makes it more sensitive to CO_2. If the deficiency of oxygen is not associated with increase of CO_2 the increased breathing will only eliminate more CO_2 thus reducing the hydrogen-ion concentration of the blood (alkalosis). Lack of oxygen is known as *anoxaemia*, and the symptoms develop as the supply of oxygen becomes deficient.

Besides the above factors, breathing is also influenced by the higher centres ; by the sensory impulses from the body surface, *e.g.* painful and thermal stimuli ; during swallowing, when the breathing becomes inhibited by impulses coming from the glosso-pharyngeal nerves from the post pharyngeal walls ; and during sleep, when the centre is depressed.

Drugs stimulating the respiratory centre.—We have already seen that alteration in the composition of the air inhaled and excess of carbon dioxide affect the respiratory centre. Any cause which tends to diminish the oxygenation of the blood, *e.g.* haemorrhage, or deficiency of haemoglobin as in anaemia or when brought about by certain drugs, stimulates the centre and increases the respiratory movements. In the same way iron, arsenic and liver extract by increasing the haemoglobin or the red blood-cells improve respiratory distress. The centre may be stimulated by certain drugs, specially strychnine, ammonia, caffeine, atropine, ephedrine, carbon dioxide gas, lobeline, camphor and the drugs commonly grouped as **analeptics**, *viz.*, leptazol, nikethamide, picrotoxin. Substances which stimulate the central nervous system also stimulate the respiratory centre. Finally, the centre may be stimulated reflexly through sensory stimulation, *e. g.* inspiration caused by application of cold to the body, inhalation of ammonia vapour or smelling salts.

Drugs depressing the respiratory centre.—The respiratory centre is more easily depressed than any of the other vital centres. In fact in most of the fatal diseases there is respiratory depression before death. Respiratory depressants make the centre less sensitive to carbon dioxide. Anaesthetics, barbiturates, narcotics, hydrocyanic acid, aconite, gelsemium, etc., depress the centre. Morphine, heroin, chloral are powerful in this respect. The cough centre being closely related to the respiratory centre, respiratory depressants also depress the cough centre and are used to check excessive coughing.

Drugs acting on the respiratory system may be discussed under the following heads, *viz.*—(a) Those which affect the respiration; (b) those which influence the bronchial secretion; (c) those which affect the bronchial muscle; (d) those which influence cough; (e) those which disinfect the respiratory passage; and (f) those that are used for radiographic examination of the lungs and the bronchial tubes.

CLASS A: Drugs which affect the respiration

CARBONEI DIOXIDUM

Carbon Dioxide. (Carbon. Diox.)

Source.—May be obtained from mineral carbonates, or from the fermentation of sugars. For convenience it may be compressed in metal cylinders.

Characters.—A heavy, colourless gas. Taste, of an aqueous solution, faintly acid. One volume of gas dissolves in about 1.3 volumes of water at 25°C.

NON-OFFICIAL PREPARATION

1. **Carbon Dioxide Snow.**—It is obtained by sudden release of liquid carbon dioxide contained in cylinders under a pressure of about 50 atmospheres. It has a temperature of −80°C. The solid snow is moulded into proper shape to suit the part which it is desired to treat. It is applied with slight pressure for from five to six seconds according to the effect desired. A short application of a few seconds causes blanching followed by hyperaemia, while prolonged application acts as a caustic and destroys diseased cells.

PHARMACOLOGY AND THERAPEUTICS

In the form of effervescent preparations CO_2 is extensively used in medicine, and many mineral waters and aerated waters contain CO_2 gas.

Locally applied, the gas or its solution acts as a mild **irritant** to the skin and mucous membrane, and if the ap-

plication is prolonged it is followed by **numbness** and **anaesthesia.** This sensory irritation leads to reflex stimulation. Carbon dioxide bath (Nauheim bath) is therefore used in many conditions of nervous and circulatory weakness, and in different diseases of the heart. Applied as a pencil (carbon dioxide snow), it not only causes anaesthesia by local freezing but also destroys the superficial tissues. It is therefore used as a **mild caustic** for superficial growths like warts, naevi, lupus, rodent ulcers, etc., in preference to other caustics ; the application is made for 5 to 40 seconds according to the size of the growth.

Internally.—The mild irritant effect is also noticed when the gas is taken internally. In the stomach it acts as a **stomachic** by increasing its vascularity and secretion ; it also helps expulsion of gas and acts as a **carminative.** Aerated water is more quickly absorbed than ordinary water and having a sharp taste is more freely taken. It is therefore a valuable **diuretic** and can be used when rapid flushing of the system is desired. Being sedative to the stomach, aerated water, or carbonic acid gas in an effervescent mixture may be used in vomiting, sea-sickness, etc.

Except when the gas is inhaled it produces no systemic effect when taken by the mouth, being mostly expelled out from the stomach by eructation. Very little is absorbed and is excreted by the lungs, and it does not alter the normal CO_2 content of the blood.

When inhaled in pure form, it causes asphyxia like any other indifferent gas, due partly to its effect on the central nervous system and partly to anoxaemia. Inhaled mixed with oxygen, it causes a rise of blood pressure; first stimulates and then depresses the respiratory, vaso-motor and vagus centres. A concentration of 5 p.c. directly stimulates the respiratory centre. By stimulating the sensory nerve-endings in the carotid sinus region and the aortic arch, it sends excitatory impulses to the respiratory centre so that CO_2 also stimulates the centre reflexly. The effects however disappear with the supply of fresh air. Stimulation generally follows the use of a concentration of $8\frac{1}{2}$ p.c., whereas a high concentration (20 to 30 p.c.) causes depression and paralysis of the vaso-motor **centre and the heart.**

Normally the respiration is regulated by the CO_2 content of the blood and the centre is sensitive to slight increase of CO_2 tension. Inhalation of oxygen with 5 p.c. CO_2 has therefore been used to **stimulate** the **respiration** and the **vaso-motor centre** in carbon monoxide poisoning, chloroform and ether anaesthesia and in narcotic poisoning. In chloroform and ether anaesthesia it stimulates breathing and accelerates absorption, thus hastens induction of anaesthesia ; given after operation it ensures

hyperventilation and deep breathing and thus helps elimination of the anaesthetic and diminishes the risk of post-anaesthetic complication (*see* page 160). It has been used successfully to control **hiccough** (30 p.c. of CO_2 to 70 p.c. of oxygen).

Five to 10 p.c. carbon dioxide in pure oxygen is a valuable means of raising the blood pressure in spinal anaesthesia provided the motor nerves of respiration are not also paralysed, when artificial respiration and vaso-constrictor stimulants are of service.

It has been used in **asphyxia** of the new-born, **drowning** and in **alcoholism** to hasten excretion by the lungs.

OXYGENIUM

Oxygen contains not less than 98 p.c. v/v of O_2. For convenience it is compressed in metal cylinders.

Characters.—A colourless, odourless and tasteless gas. One volume dissolves in about 43 volumes of water, and in 3.6 volumes of alcohol (95 p.c.).

ACTION AND USES

Oxygen, though present in small proportion (20 p.c.) as compared to nitrogen, is the most important constituent of air. An increase of this proportion or even inhalation of pure oxygen produces no noticeable effect under normal conditions, and the oxidation in the tissues is not increased nor metabolism modified, but tends to raise the blood pressure and causes a slowing of the heart by producing sinus bradycardia.

Oxygen has a distinct value in cases where there is lack of oxygen in the body, *i.e.* **anoxaemia** is present. This may arise from (*a*) when the tension of oxygen in the arterial blood is less than normal, so that there is less oxygen in the haemoglobin (anoxic type) ; (*b*) when the oxygen tension in the blood is normal but the quantity of functional haemoglobin is too small (anaemic type) ; as happens in different types of anaemia, or when methaemoglobin or carboxyhaemoglobin is found in the blood ; as happens in carbon monoxide poisoning and poisoning by nitrites, acetanilide or sulphanilamide ; and (*c*) when there is defective supply of oxygen in the tissues (stagnant type) ; as happens in chronic heart disease, circulatory failure, shock or haemorrhage. At high altitudes the atmospheric oxygen tension is less and there is increased formation of red blood-cells and increased anabolism in other tissues, specially the muscles.

The function of oxygen therapy is not to attack the underlying causes of the disease, but to give the patient the benefit of as high a blood oxygen saturation as possible. It is no doubt possible that some of the benefits of oxygen therapy may be obtained by other therapeutic

measures apart from the improvement of arterial anoxaemia.

It is useful in those forms of **asphyxia** due to the interference with the access of oxygen to the blood, *e.g.* in pneumonia (due to diminished absorbing surface of the lung), croup, drowning (due to mechanical interference with respiration), in collapse of anaesthesia (due to depressed respiration), etc. Similarly it is useful when there is deficiency in the actual quantity of haemoglobin, as in certain forms of anaemia. Here it increases the oxygen carried in solution by the plasma and not by increasing the quantity of oxygen carried by the haemoglobin. It is also useful in advanced heart disease when the supply of oxygen to the tissues is impaired from circulatory failure ; in anoxic conditions as may occur in mountain sickness due to insufficient pressure of oxygen in the inspired air ; and in pulmonary oedema.

It is of undoubted value in **coronary thrombosis.** A concentration of 50 p.c. will aid in maintaining an adequate oxygen supply to the tissues of the body until the heart has had an opportunity to recover from its functional disturbance.

Mode of administration.—For therapeutic purposes oxygen can be obtained in cylinders, and the usual method to pass the tube connected with the cylinder through water and then deliver through a glass funnel which is held near the patient's nose, or put into the mouth or into the nose by a rubber catheter with extra holes at the top, is unsatisfactory and wasteful. With the funnel method the flow is too low for effective action, and the strapping a catheter to the cheek is uncomfortable to the patient. Moreover the custom of giving oxygen intermittently for a few minutes at a time is illogical and harmful. To be effective it must be continuous so long as indications for oxygen exist.

Many varieties of appliances for administration of oxygen are available, the underlying principle being efficiency, comfort and simplicity in working. When used by the nasal route, the catheter should be of soft rubber and should be lubricated with some bland oil. A 1 p. c. cocaine ointment is useful. The catheter should be passed to the back of the nose and the free end carried upwards to the forehead and fixed with adhesive tape. Maximum effect is obtained by the use of B. L. B. mask devised by Boothby, Lovelace and Bulbulian of the Mayo Clinic which is most efficient, economical and convenient.

In order that oxygen may be of any use it is necessary that it should be given before any marked signs of cyanosis appear when giving to patients suffering from pneumonia. Ordinarily three bubbles a second when passed through water yield 0.2 litre per minute. The amount of oxygen required is double the amount that a fever patient normally takes, *i. e.* 2 litres per minute.

Subcutaneous injection is considered by French physicians as the route of choice, and it is claimed that when given by this method the effects are more pronounced, as a definite amount is supplied to the system promptly. In bad cases of asphyxia 500 c. c. is quite suitable. Subcutaneous emphysema may appear and is of no consequence.

CLASS B : Drugs which influence the bronchial secretion

1. Expectorants

Expectorants are drugs which increase bronchial secretion and help its expulsion. To appreciate this action it is necessary to understand the natural mechanisms for protecting the air passages. They are *motor* and *secretory.* The motor mechanism consists of (1) propulsive movement of the cilia which line the mucous membrane ; (2) reflex expulsive mechanism of cough ; and (3) peristaltic movements of the muscles of the smaller bronchi. The secretory mechanism keeps the bronchial surface moist and dilutes irritating substances. The mucous membrane therefore is supplied with a large number of glands. Both these functions, *viz.*, the motor and secretory, are regulated by the vagus and sympathetic nerves. The afferent fibres of the vagus transmit impulses from the mucous membrane, while the efferent fibres supply the muscles and the secretory glands. The muscles are also supplied by the efferent fibres of the sympathetic. Both these sets of fibres converge upon a hypothetical *cough centre* which is related to the respiratory and vomiting centres.

Gunn has classified expectorants as follows : *

1. *Reflex expectorants.*—Most of the expectorants belong to this class. They act by stimulating the sensory ends of the vagus in the stomach and when given in large doses act as emetics. To this class belong tartar emetic, ipecacuanha, senega, quillaia, squill, ammonia, bicarbonate of ammonia, alkalies, apomorphine and camphor. The centre for bronchial secretion being closely associated with the vomiting centre in the medulla, emetics in sub-emetic doses act as expectorants.

Similarly stimulation of the sensory endings of the vagus in the bronchial mucous membrane also increases bronchial secretion. Volatile oils, oleo-resins, balsams, etc., act in this way. These produce mild irritation during excretion through the bronchial mucous membrane.

2. *Central expectorants.*—To this class belongs apomorphine, which increases the secretion by stimulating the centre. Ipecacuanha and tartar emetic may have a central effect.

3. *Acting by stimulating the bronchial glands.*—Iodides increase secretion of the bronchial mucus by acting on the secreting cells during excretion. It was formerly believed that most expectorants, specially ammonium chloride and alkalies, acted by increasing the secretion of bronchial glands.

Administration of expectorants depends upon a proper appreciation of the condition of the patient, the type of cough, the character of the sputum and the correlation with the stages and clinical features of the causative diseases.

Expectorants may be therapeutically classified as follows :—

I. **Stimulant expectorants.**—These are excreted by the bronchial mucous membrane which is mildly irritated resulting in increased bronchial secretion. This mild irritation is supposed to help

* *British Medical Journal,* Vol. II, 1927.

repair. The drugs belonging to this group are mostly volatile oils and aromatics, and Sollmann calls these *aromatic expectorants*. They are volatile oils, terebene, balsam of Peru and tolu, camphor, benzoates, creosote, guaiacol, etc.

II. Sedative expectorants.—These are specially selected to check excessive or harassing cough. They belong to different classes and act in the following ways :—

(1) By soothing acute inflammation or irritation by increasing the secretion of protective mucus in the bronchioles without directly irritating the mucous membrane. They are chiefly the *reflex expectorants*, also called *nauseant expectorants*. They are tartar emetic, ipecacuanha, apomorphine, etc. *Demulcents*, like liquorice, acacia, glycerin, etc., also act as sedatives.

(2) By liquefying thick tenacious mucus. To this class belong the salines like potassium iodide, chloride of ammonium and bicarbonates of ammonium, potassium and sodium, etc. These are also called *saline expectorants*.

(3) By controlling excessive cough reflex. They are mostly preparations of belladonna, and opium or its alkaloids, *e.g.* tinct. opii camph., pulv. ipecac. et opii, codeine, dionin, etc. Since they reduce the secretion they should not be used when the secretion is profuse. These are also known as *anodyne expectorants*. Syr. prun. serot. also acts as a sedative expectorant.

III. **Antispasmodic expectorants.**—Although these do not act as true expectorants inasmuch as they do not increase the secretion of mucus or make it less viscid, they help expulsion of mucus by relaxing the bronchial muscles and are of great value in bronchial asthma, and chronic bronchitis. They are belladonna, lobelia, nitrites, grindelia, ephedrine and adrenaline.

2. **Anti-expectorants** are drugs which diminish the bronchial secretion. They are rarely used therapeutically. Opium, morphine, belladonna, codeine reduce secretion.

IPECACUANHA

Ipecacuanha. (Ipecac.).

Syn.—Ipecacuanhae Radix ; Hippo.

Source.—The dried root, or the rhizome and root, of *Cephaelis Ipecacuanha*, known in commerce as Rio or Brazilian Ipecacuanha, or of *Cephaelis acuminata*, known in commerce as Cartagena, Nicaragua, or Panama Ipecacuanha. Contains not less than 2 p.c. of the total alkaloids, calculated as *emetine*.

Characters. Tortuous pieces, up to 15 cm. long, and 6 mm. thick, colour, dark brick-red or brown, closely annulated. Fractured surface exhibits a wide greyish bark and a dense central portion. Odour, slight. Taste, bitter.

Composition.—Three alkaloids from 2 to 3 p. c. ; of these (1) *Emetine* 72 p. c. (2) *Cephaeline* 26 p. c. (3) *Psychotrine* 2 p. c. (4) Methylpsychotrine and emetamine, present in small proportion. (5) Ipecacuanhic or cephaelic acid. (6) Starch, volatile oil, gum, etc.

Ipecacuanhae Pulvis. (Ipecac. Pulv.). Powdered Ipecacuanha.—Light-grey to yellowish-brown powder.

Official Preparations

1. **Extractum Ipecacuanhae Liquidum.**—Contains 2 p. c. w/v of the alkaloid emetine, or 1/25 gr. in 2 ms. B. P. Dose.—1/2 to 2 ms. or 0.03 to 0.12 mil. ; 10 to 30 ms. or 0.6 to 2 mils as emetic.

2. **Tinctura Ipecacuanhae.**—Contains 0.1 p. c. w/v emetine. 1/30 gr. in 30 ms. B. P. Dose.—10 to 30 ms. or 0.6 to 2 mils ; 1/2 to 1 oz. or 15 to 30 mils as emetic.

Ipecacuanha Praeparata. (Ipecac. Praep.). Syn.—Ipecacuanha Pulverata. Prepared Ipecacuanha is ipecacuanha reduced to a fine powder, and adjusted if necessary by the admixture in suitable proportions of powdered exhausted ipecacuanha, or by the addition of

powdered lactose, to contain 2 p.c. of the total alkaloids calculated as *emetine*. Contains 1/25 gr. emetine in 2 grs.

B. P. Dose.—1/2 to 2 grs. : or 30 to 120 mg. ; 15 to 30 grs. or 1 to 2 grms. as emetic.

Official Preparations

1. **Pulvis Ipecacuanhae et Opii.** *Syn.—Pulvis Ipecacuanhae Co., Dover's Powder.*—Contains 1/10 gr. morphine in 10 grs. or 10 p. c. of powdered opium. **B. P. Dose.**—5 to 10 grs. or 0.3 to 0.6 grm.

(a) **Tabellae Acidi Acetylsalicylici cum Ipecacuanha et Opii.** *Syn.—Tablets of Aspirin and Dover's Powder.*—**B. P. Dose.**—1 to 2 tablets. Contains 2½ gr. each of Dover's powder and aspirin.

(b) **Tabellae Ipecacuanhae et Opii.** *Syn.—Dover's Powder Tablets.*—**B. P. Dose.**—5 to 10 grs. or 0.3 to 0.6 grm. N. B. If the quantity in each tablet is not mentioned, 5 gr. tablets shall be supplied.

2. **Trochisci Morphinae et Ipecacuanhae.**—Contains 1/32 gr. of morphine hydrochloride and 1/10 gr. of ipecacuanha in each.

EMETINAE HYDROCHLORIDUM. (Emet. Hydrochlor.).—Emetine Hydrochloride is the hydrochloride of an alkaloid, emetine, obtained from ipecacuanha or prepared by the methylation of cephaeline.

Characters.—Colourless, crystalline powder ; odourless ; taste, bitter. *Soluble* in water and in alcohol (90 p. c.).

B. P. Dose.—1/2 to 1 gr. or 30 to 60 mg. by subcutaneous or intramuscular injection.

Official Preparations

1. **Emetinae et Bismuthi Iodidum.**—A complex iodide of emetine and of bismuth. Contains 25.0 to 29.0 p. c. of emetine, and 18.0 to 22.0 p. c. of Bi. A reddish-orange powder. Odourless ; taste, bitter, acrid. Insoluble in water. **B. P. Dose.**—1 to 3 grs. or 60 to 200 mg. daily.

2. **Injectio Emetinae Hydrochloridi.**—**B. P. Dose.**—By subcutaneous or intramuscular injection : 1/2 to 1 gr. or 30 to 60 mg. daily. N. B. When no strength is stated, 1 gr. in 15 ms. shall be dispensed.

Non-official Preparation

1. **Emetine Periodile.** ($C_{29}H_{40}N_2O_4I_6$).—Introduced as a substitute for emetine-bismuth-iodide. Contains 38.7 p. c. of emetine. Can be given by the mouth without any local effect. Completely insoluble in weak acids. Dissolved and split up by weak alkalies. Supposed to be most effective and least toxic of all emetine preparations. Useful in refractory cases of amoebic dysentery. *Dose.*—2 grs. (0.12 grm.), thrice daily after food for 15 days.

Pharmacology

Externally.—Powdered ipecacuanha acts as an irritant, rubefacient and pustulant on the unbroken skin. A solution of emetine 1 in 5000 kills amoebae in broth cultures ; stronger solutions (1 in 100 to 1000) are necessary for organisms in bits of mucus from the intestine. It kills anthrax bacillus.

Internally. **Alimentary system.**—Ipecacuanha has an unpleasant bitter taste and excites the flow of saliva. Small doses (¼ to ½ gr.) stimulate the local circulation, increase the secretion of the gastric juice and act as a stomachic. Large doses (15 to 30 grs. of ipecacuanha or ½ to 1 gr. of emetine) produce vomiting. Emesis may also sometimes occur after parenteral administration of emetine. Eggleston and Hatcher consider that vomiting is both reflex and central. Injected intravenously into pigeons it does not cause emesis. Vomiting, which is a late effect after injection of emetine in man, may be either reflex from the heart or from the irritant effect of the drug

excreted into the stomach. In drop doses ipecacuanha tincture acts as an antiemetic.

The same irritant effect is also observed in the intestine and emetine causes stimulation of the automatic movements. With larger doses this stimulation is not observed, while in some cases depression follows. Diarrhoea, observed sometimes during a course of emetine treatment, may be ascribed to this irritant effect of the drug excreted into the gut and also to increased accumulation of fluid from local vaso-dilatation.

The local irritant effect of the drug precludes the oral use of emetine hydrochloride in the treatment of amoebiasis except as emetine-bismuth-iodide.

Emetine is believed to possess a direct stimulant action on the liver, producing a plentiful secretion of bile.

Heart and circulation.—Emetine makes the heart weak, slow and irregular. Within certain limits the heart returns to normal after the initial depression. With larger doses,

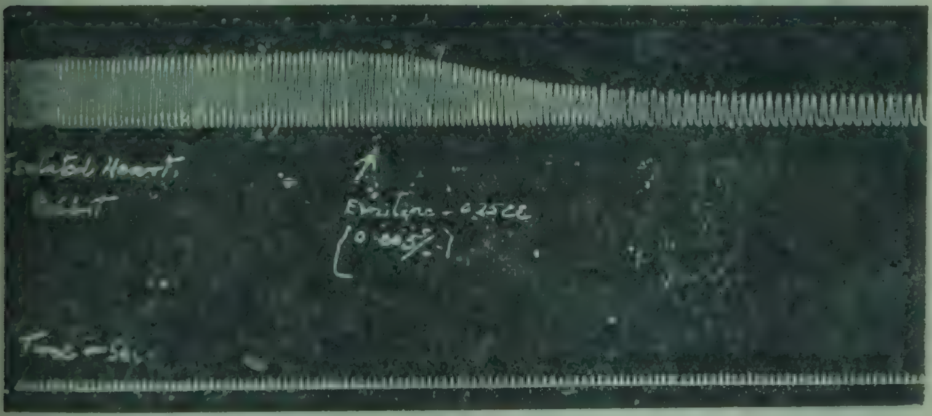


Fig. [illegible].—Tracing of the Movements of the Isolated Rabbit's Heart during Perfusion. At the point of arrow 0.25 c. c. of 0.005 p. c. solution of emetine hydrochloride was introduced into the fluid. Note weakening and slowing of the heart. The force of systole getting weaker and weaker. Upstroke, systole.

the heart fails to recover—auricular and ventricular dissociation may be induced and death may occur from auricular and ventricular fibrillation—the heart finally stopping in diastole. All these effects are due to direct action of the drug on the cardiac muscle. The auricle in mammal is early affected and the effect is greater than on the ventricle, whereas opposite effects are noticed in frogs. Further, repetition of the original dose, even long after the initial depression has passed off, produces a greater effect. Vagotomy or previous use of atropine has no influence on the above effects.*

The blood pressure falls which is proportionally greater

* S. N. Ghosh and P. Adhya, *Jour. Ind. Med. Assoc.*, Nov. 1943.

with larger doses. Here again, as in the case of the heart, repetition of the same dose, even after considerable interval leads to progressively greater fall. An increase in the volume of the limb and of the splanchnic area occurs *pari passu* with the fall of blood pressure but regaining of the original condition always follows the restoration of the pressure to the normal level. The 'lag' in recovery perhaps indicates that emetine leaves a residual effect which adds to the effect of the subsequent doses of the drug. This possibly explains the relatively greater depression of the heart and blood pressure with repeated doses. Perfusion of frog's vessels does not suggest any direct action on the vessel wall. The fall of blood pressure is possibly due to cardiac depression, although the possibility of a central effect on the vaso-motor centre causing wide-spread vaso-dilatation cannot be wholly ignored.

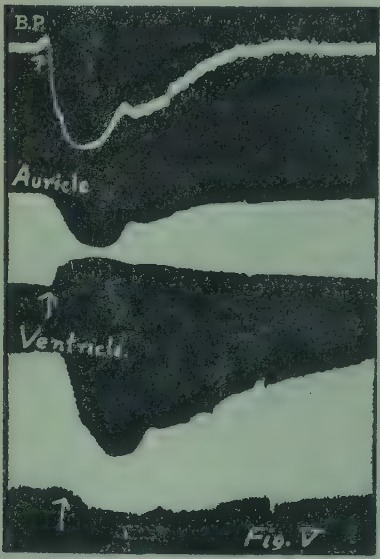


Fig. 24.—Cat under chloralose. Showing effect of emetine on blood pressure, and on auricular and ventricular contraction. Note—Profound fall of blood pressure associated with depression of the auricle and ventricle, the auricle being more affected than the ventricle.

In toxic doses the vessels dilate, while non-toxic doses given intravenously lower carotid pressure but increase pulmonary pressure.

Nervous system.—In frog it produces a slowly advancing central paralysis. In man there is a general depression producing weakness and lethargy, or there may be neuritis. In toxic doses there is degeneration of the anterior horn cells.

Respiratory tract.—It is an **expectorant** acting reflexly through the stomach. During elimination it also stimulates the bronchial mucous membrane and renders the secretion more fluid. Toxic doses of emetine have a tendency to produce pulmonary congestion, or to haemorrhagic pneumonic consolidation.

Skin.—Moderate doses ($\frac{1}{2}$ to 1 gr.) of ipecacuanha stimulate the skin and produce **diaphoresis,** which action is increased by the combination with opium (Dover's powder).

Uterus.—It has been suggested that emetine should be avoided during pregnancy as it may cause abortion. Experiments with strips of rabbit's uterus have shown that emetine in dilutions of 1 in 150,000 to 1 in 100,000. the concentration attained after a dose of one grain in

man, assuming that the whole of the alkaloid is in solution, has very little effect on the uterus. Since emetine does not produce contraction of the uterus it cannot be a factor in causing abortion, which is probably due to bacterial toxin and not to emetine.*

Acute toxic action.—Emetine is cumulative. Severe diarrhoea, abdominal pain, tenesmus and toxic delirium have been reported from $\frac{1}{2}$ gr. doses used for four days. Spehl and Collard noticed flaccid paralysis of the muscles of the neck with dysphagia and difficulty of mastication and speech, oedema of the face, and rapid, weak heart from 22 grs. given in 18 days. Acute renal insufficiency, general oedema, haemoptysis, flaccid paralysis, peripheral neuritis, delirium, coma, and failure of the heart are the toxic symptoms.

THERAPEUTICS

Internally. **Alimentary canal.**—As a stomachic tonic, powdered ipecacuanha ($\frac{1}{4}$ to $\frac{1}{2}$ gr.) is used with other stomachics and bitters in **atonic dyspepsia.** Ipecacuanha tincture in 1 minim doses, every quarter to half hour, checks the vomiting of pregnancy and gastric irritability during febrile attacks and other diseases. Ipecacuanha is not a suitable emetic in poisoning as its action is tardy, but it is exceedingly efficacious in **croup** and **bronchitis** of children, not only by mechanically expelling the mucus, but by its influence on the respiratory mucous membrane. Sixty to 120 ms. of the tincture should be given every 1 or 2 hours until the child vomits.

Powdered ipecacuanha in 20, 30 or even 60 or 90 gr. doses was formerly used in the treatment of acute amoebic dysentery, but it had the drawback of producing nausea and vomiting. Both in **acute hepatitis** and in **amoebic dysentery** the treatment by ipecacuanha *per os* has been replaced by the daily subcutaneous injection of emetine hydrochloride in doses varying from $\frac{1}{4}$ gr. to 1 gr., the most effective dose for adults being 1 gr. and not more than ten injections should be given in one course. It is however desirable that *six injections* should be given to be followed by rest for three to six days and then repeated. After this at least two weeks interval should be given before it is administered again. In effecting a cure co-operation of the host is necessary, and it is possible that the reticulo-endothelial system plays an important part (*see* page 52). Emetine treatment should be accompanied by the administration of bismuth carbonate as its effects are better if the reaction of the gut is rendered alkaline. In both these diseases pain, tenderness and fever in hepatitis, and blood, mucus and tenesmus in dysentery, rapidly disappear. It should be remembered that emetine is a cumulative and highly poisonous drug, and its prolonged use is followed by diarrhoea,

* R. N. Chopra and B. N. Ghosh. *Indian Medical Gazette*, 1922.

lassitude, general weakness, paralysis of muscles, and weakness of the heart. There may be peripheral neuritis with weakness or even paralysis of extremities, but this is very rare. The administration of the remedy should be stopped on the appearance of any of the toxic symptoms.

Recently much doubt has been thrown on the specificity of emetine. Cases are on record where relapses have occurred after several courses of the drug, and it has been pointed out that when patients were excessively dosed with emetine the amoebae become resistant, though this supposition does not rest on scientific observation. It has been suggested that these apparently resistant cases are due to wide spread secondary bowel infection.

Emetine exerts no effect upon the pre-cystic and cystic forms of *E. histolytica*, such as are found in the chronic stage of the disease where emetine-bismuth-iodide is useful when given in gelatin capsules. Sugar-coated tablets pass unchanged through the intestinal canal. It should be given by the mouth at bed time. The object being to enable the drug to pass through the stomach unchanged and to liberate emetine in the intestine where it will unfold its action directly on the entamoeba, while emetine given hypodermically does not reach the part in sufficient concentration to be active. It is generally given in doses of 3 grs., but 2 gr. dose is better tolerated, causes less depression and is equally effective. It should be given three hours after the last meal at bed time. Vomiting is avoided by giving a dose of phenobarbitone one hour before, or by giving tincture of opium. The results are however disappointing ; while some cases respond to this drug others require the use of either acetarsone (stovarsol), carbarsone, or chiniofonum. In subacute and chronic cases and diarrhoea, Dover's powder acts well.

Emetine is also used in the treatment of **bilharziasis** with success, though not so efficacious as antimony. Since amoebic dysentery may also be a common complication of this disease, its use serves the double purpose, and it can be used in cases with advanced renal and hepatic disease or in those intolerant to antimony. It may be used *intravenously*, but in complicated cases should be used *intramuscularly*. The usual dose for intravenous use is 0.06 grm. the 1st day, 0.09 grm. 2nd day, and then 0.1 grm. on the 3rd, 5th, 7th, and 10th days with a total of 0.75 grm. It has also been recommended in **dracontiasis**.

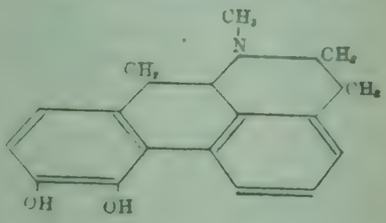
Ipecacuanha is a most effective remedy for catarrhal jaundice and torpidity of the liver when given alone or combined with other cholagogues, and is a favourite constituent of aperient and cathartic pills.

Respiratory passages.—As an expectorant ipecacuanha, in the form of tincture, liquid extract, lozenge or syrup, is daily used in different inflammatory conditions of the respiratory passages, e.g. in cold, catarrh, acute and

chronic bronchitis and broncho-pneumonia. In these conditions it is used in smaller doses so as not to induce emesis. Ipecacuanha is also recommended in hay asthma and whooping cough.

Emetine has been used in haemoptysis, but clinical results are not very encouraging unless accompanied with a high blood pressure ; on the other hand there is risk of pulmonary congestion.

APOMORPHINAE HYDROCHLORIDUM. (Apomorph. Hydrochlor.).—Apomorphine Hydrochloride is the hydrochloride of an alkaloid apomorphine obtained from morphine by the abstraction of the elements of a molecule of water.



Characters.—Minute, glistening crystals ; colourless or greyish-white, turning greenish on exposure to light and air ; neutral. *Solubility.*—1 in 50 of water, in alcohol (90 p. c.), sparingly soluble in solvent ether, and in chloroform.

B. P. Dose.—1/32 to 1/8 gr. or 2 to 8 mg. as an emetic by subcutaneous injection.

Official Preparation

1. **Injectio Apomorphinae Hydrochloridi. B. P. Dose.**—1/32 to 1/8 gr. or 2 to 8 mg. as *emetic subcutaneously.* N. B. When no strength is stated, a solution of 1/20 gr. in 15 ms. should be dispensed.

Pharmacology

Internally. **Stomach.**—Apomorphine is a reliable emetic acting directly on the vomiting centre. It acts within 10 to 15 minutes with the usual attendant symptoms of vomiting, viz., salivation, increased secretion from the nose, throat and bronchial passages, and cold perspiration. These effects, however, are not due to any direct action of the drug on the stomach. The central effect was proved by Eggleston and Hatcher by injecting into animals from which the whole alimentary canal from the cardia to the anus was removed but who showed typical retching, vomiting movements and expulsion of mucus from the mouth and oesophagus. On the other hand direct application of the drug to the oesophagus or pharynx did not produce vomiting although emesis occurred in animals if the drug was applied directly to the floor of the fourth ventricle in the region of the vomiting centre. It does not irritate the stomach, and produces emesis when other emetics given by the mouth fail. One-third grain given per rectum also induces vomiting.

Heart and circulation.—In medicinal doses it has no action on the heart and blood-vessels, beyond a slight depression from the effect of vomiting, but in large doses it increases the frequency of the pulse, probably by stimulating the accelerator nerves.

Respiration.—Like all emetics, when given in small

doses, it increases the secretion of bronchial mucus an makes it less viscid. This hypersecretion is also due t its direct action on the cough centre. Very large dose paralyse the central nervous system, death takes plac from respiratory failure although the heart continues t beat for some time.

Nervous system.—In large doses apomorphine pro duces excitement in animals which do not vomit. Th respiration becomes quickened, but remains regular. I toxic doses there is ataxia and violent and irregular con vulsions. In non-emetic doses it often induces sleep, an when given hypodermically in emetic doses it acts as narcotic.

THERAPEUTICS

Internally.—As a prompt and certain **emetic,** apomor phine is used in poisoning, *i.e.* in narcotic poisoning drunkenness, etc. For this purpose $\frac{1}{10}$ gr. hypodermicall acts within 1 to 2 minutes ; although given by the mout it may produce vomiting after absorption, but large dose are necessary. As an **expectorant,** it is always given b the mouth. In the early stage of the inflammation of th larynx, trachea and bronchi, when the mucous membran is dry or secretes a viscid tenacious mucus, apomorphin loosens the secretion and removes inflammation. In crou and acute bronchitis of children it is useful. In subacut or chronic bronchitis, broncho-pneumonia, chronic catarr of large tubes, it is most useful if the secretion is scant and tenacious. Sometimes it can be usefully combine with codeine in the form of a linctus with syrup of wil cherry, syrup of tar or of lemon.* It is valuable in per sistent **hiccough.** One injection of $\frac{1}{10}$ gr. often give permanent relief.

It is sometimes used in small sub-emetic doses hypoder mically as a sedative without producing vomiting if th dose is not exceeded beyond $\frac{1}{32}$ gr. and has been used i alcoholic excitement and delirium tremens.

Caution.—It should be given with great caution to the feebl the aged, the children, and to those subject to chronic diseases o the heart and lungs.

SENEGA. (Seneg.).—Senega is the dried root of *Polygal Senega.*

Characters.—Greyish or brownish-yellow, slender, from 5 to 20 cm. long, an 3 to 6 mm. wide, with a knotty crown bearing the bases of numerous slender aeri stems ; frequently curved or contorted, sparingly branched, keeled, sometim transversely wrinkled.

Composition.—It contains two glycosidal saponins, *viz*—(1) *Senegin*, and (

* Apomorph. hydrochlor.	gr. 1
Syr. prun. serot.	oz. 1½
Syr. picis liq.	oz. 1½

One teaspoonful three or four times a day.

* Apomorph. hydrochlor.	gr. 1/6
Codein. phosph.	gr. 1/2
Syr. prun. serot.	ad. oz. 1

One teaspoonful as linctus.

[illegible] which resemble but are not identical with *Quillaja-sapotoxin*, the active principle of *quillaja bark*.

Senegae Pulvis. (Seneg. Pulv.).—Powdered Senega.

Official Preparations

1. **Extractum Senegae Liquidum.—B. P. Dose.—5 to 15 ms. or 0.3 to 1 mil.**
2. **Tinctura Senegae.—B. P. Dose.—30 to 60 ms. or 2 to 4 mils.**
3. **Infusum Senegae Concentratum.—B. P. Dose.—30 to 60 ms. or 2 to 4 mils.**
4. **Infusum Senegae.— B. P. Dose.—1/2 to 1 oz. or 15 to 30 mils.**

Pharmacology

The action of senega depends chiefly on the presence of senegin which resembles sapotoxin. These saponins form froth when shaken with water and emulsify oils and resinous substances. They are mixtures of various, generally colloidal, substances of a glycosidal nature which produce much local irritation when used subcutaneously. They are not absorbed by the healthy epithelium of the alimentary tract and are decomposed by the alkalies and ferments into inert compounds. Introduced directly into the blood in large doses they cause convulsions and respiratory failure which may cause death. Small doses produce gastro-intestinal irritation with symptoms resembling dysentery. They are specially destructive to red blood cells and set free haemoglobin into the serum. This effect is due to their affinity for cholesterin, and if they are saturated with cholesterin they lose this haemolytic property.

When inhaled, senega causes sneezing and cough. Taken by the mouth it acts as an expectorant, due chiefly to its nauseant effect. Senegin is excreted through the bronchial mucous membrane and during excretion increases the secretion.

Therapeutics

The chief use of senega is as an **expectorant** in acute and chronic bronchitis and in pneumonia in the stage of resolution. It is of value in bronchiectasis. The best effects are obtained when senega is combined with ammonium bicarbonate.

Very small doses of senega (3 ms. of tincture to ½ oz.) emulsify fats and oils, and the tincture may be used with advantage in making castor oil emulsion.

QUILLAIA. (Quill.) **Syn.**—Quillaiae Cortex; Panama Bark; Soap Bark.—Quillaia is the dried inner part of the bark of *Quillaja saponaria*, and of other species of *Quillaja*.

Character.—Flat pieces, up to about one metre long, 20 cm. broad, and 3 to [illegible] considerably in length and width. Outer surface brownish-[illegible], inner surface smooth, white or yellowish-white. Taste, pungent, acrid, powder irritates nostrils.

Composition.—(1) *Quillaia-sapotoxin*, and (2) *Quillajic acid*, toxic glycosides, closely allied to saponin.

Quillaiae Pulvis. (Quill. Pulv.).—Powdered Quillaia is pale buff with a pink tinge.

Enters into.—Liq. Picis Carbonis.

Official Preparation

1. **Extractum Quillaiae Liquidum.**—Enters into the preparation of Emuls Chloroformi and Emulsio Menthae Piperitae.

Pharmacology and Therapeutics

Externally.—The powder soap bark is very irritant t the nostrils, giving rise to a nasal discharge, sneezing, a sometimes cough. It is sometimes used as a sternutator

Internally.—Quillaia bark contains five times mo *saponin* or senegin than senega, and is therefore a mo powerful expectorant. It is rarely used internally. B cause it contains a large percentage of saponin, it employed for emulsifying resins and oils.

Class C: Drugs which influence the bronchial muscles

Bronchial Antispasmodics

These drugs when used either as inhalation or by the mou relieve respiratory spasm by relaxing the bronchial muscles. T bronchial muscles are supplied by the parasympathetic (vagu which constricts, and sympathetic which dilates. Relaxation of t bronchial muscle is indicated in asthma. The spasm is relieved atropine, hyoscine, etc., which depress the vagal endings; by lobel which depresses the vagus nerve-endings or the ganglia; by adr naline and ephedrine which stimulate the sympathetic nerve-ending by nitrites and papaverine, which depress the muscle. Narcoti cause relaxation of the muscle by depressing the centre. Morphi in small doses also cause relaxation of the bronchial muscl Smoking of stramonium or datura cigarettes, or inhalation of smo of nitre papers will often give temporary relief. Unfortunate atropine, though relaxes the bronchial muscles and thus reliev spasm, has the drawback of diminishing bronchial secretion, whi the sympathetic stimulants like adrenaline do not.

The Bronchial Antispasmodics are:

Lobelia, **Adrenaline** (*see* page 305), **Ephedrine** (*see* page 312), **Atropine** (page 248), **Nitrites** (*see* page 322), **Grindelia**.

Lobelia. (Lobel.), I. P. L. Syn.—Lobelia Herba.—Lobelia co sits of the dried aerial parts of *Lobelia nicotianifolia*, collected October and November and dried in the shade.

Characters.—Stems, rounded, channelled, furnished with narrow wing purplish hairy, scarred. Leaves irregularly toothed and hairy. Capsules, infla two-celled containing brown seeds. Odour irritating. Taste, at first slight, a chewing, burning and acrid.

Composition.—It contains (1) *Lobeline*, an oily, volatile alkaloid, crystalli in broad, colourless needles. (2) *Lobelic acid.*

Dose.—1 to 3 grs. or 0.06 to 0.2 grm.

Non-official Preparations

1. **Tinctura Lobeliae Aetherea I. P. L.**—Contains 0.06 p.c. w v of the to alkaloids of lobelia, *lobeline*. *Dose.*—5 to 15 ms. or 0.3 to 1 mil.

2. **Lobeline Hydrochloride, B.P.C.**—The hydrochloride of the alkaloid deri from *Lobelia*. A white crystalline powder, soluble 1 in 40 of water, 1 in 12 alcohol (95 p.c.). Solution should not be heated. A powerful respiratory sti lant. *Dose.*—1/20 to 3/20 gr. or 3 to 9 mg. by *injection*.

Pharmacology

The action of lobelia is due to the presence of the alkaloid lo line which resembles nicotine in its effects. It first stimulates a

then depresses the parasympathetic ganglia. An injection of lobeline therefore causes increased salivary and bronchial secretion, constriction of the bronchial muscle, increased intestinal movements, slowing of the heart and a rise of blood pressure. These effects however pass off soon and are followed by opposite effects.

Gastro-intestinal canal.—In large doses it produces gastro-intestinal irritation, causing vomiting, purging and great prostration. The vomiting is probably due to the stimulation of the vomiting centre.

Heart and circulation.—After the initial rise there is fall of blood pressure. In cases of weak heart this effect may arrest it altogether. Usually however the heart returns to normal or there may be acceleration. These effects are due to the direct action on the muscle and on the vagus ganglia.

Respiration.—The bronchial muscles are relaxed and the effect is due to depression of the vagus endings or their ganglia. There may be an initial constriction from stimulation of the vagus ganglia. Lobeline lessens the CO_2 threshold and stimulates the respiratory centre causing considerable increase in pulmonary ventilation.

THERAPEUTICS

For its powerful bronchial antispasmodic action it is used in **asthma**. Large doses sometimes cause great depression. If there is more or less dyspnoea throughout 24 hours the patient must have 10 ms. thrice daily, besides a few extra doses during the paroxysm. Often speedier relief is obtained by combining it with bromides and iodides.*

It is used in spasmodic bronchitis and whooping-cough, relieving the paroxysmal dyspnoea and spasms.

Because it stimulates the respiratory centre, lobeline is used in pneumonia, poisoning by carbon monoxide and morphine, and in the asphyxia of the new born. It may also be used in any case of *sudden respiratory failure* and may be combined with cardiac stimulants. The usual dose is 1/20 gr. (3 mg.) hypodermically. It may be used intravenously in cases of extreme urgency, but since it produces other side-effects, specially on the heart, it should be used with caution in patients with weak myocardium.

GRINDELIA, B.P.C. (*Not official*).—Dried leaves and flowering tops of *Grindelia camporum.*

Composition.—(1) *Amorphous resins* (20 p.c.) (2) *Heptriacontane*, a crystalline [illegible], various glycerides, *l*-dextrose, tannin, colouring matter and a trace of volatile oil.

NON-OFFICIAL PREPARATION

1. **Extractum Grindeliae Liquidum, B. P. C.**—1 in 1. *Dose.*—**10 to 20 ms.** or **0.6 to 1.2 mils.**

PHARMACOLOGY AND THERAPEUTICS

Grindelia acts as a mild stomachic, and if continued too long it may cause gastric uneasiness.

After absorption it slows the heart and respiration, but its chief action is on the bronchial mucous membrane which it stimulates, and on the bronchial muscles, which it relaxes. It is therefore an expectorant and a bronchial antispasmodic. In large doses it powerfully depresses the respiratory and cardiac centres, dilates the pupil and causes sleep.

* Pot. brom.	gr. 120
Pot. iod.	gr. 120
Tinct. lobel. ether.	ms. 180
Tinct. bellad.	ms. 60
Aqua chlorof.	ad. oz. 6

1/2 an ounce three or four times a day.

Its chief use is in **asthma**, 20 or 30 ms. of the liquid extract given every half or one hour relieve a paroxysm after two, three or four doses. The dried leaves mixed with nitre may be burnt and the fumes inhaled with advantage. It is useful in spasmodic bronchitis, whooping-cough and other spasmodic respiratory troubles.

CLASS D : Drugs which influence cough

Bronchial Sedatives

Coughing is a reflex act intended to remove some source of irritation from the upper air passages. Persistent and ineffective cough, due to irritation of the throat or tenacious mucus, frequently gives trouble. Dry hacking cough is also common in phthisis. For relief of cough belladonna, opium, heroin, codeine, dionin and wild cherry bark are indicated.

PRUNUS SEROTINA. (Prun. Serot.). **Syn.**—Pruni Virginianae Cortex.—Wild Cherry Bark is the dried bark of *Prunus serotina,* collected in autumn.

Characters.—Curved or channelled pieces or irregular fragments, about 3 mm. thick. Young bark smooth, reddish-brown, marked with transversely elongated lenticels, and granular fracture. Old bark rough and nut-brown. Taste, astringent, aromatic and bitter. Odour after maceration with water, like bitter almonds.

Composition.—(1) *d-mandelonitrile* (*prunasin*) a glycoside ; and (2) an enzyme *prunase* which yield hydrocyanic acid, *benzaldehyde* and dextrose in the presence of water. (3) A bitter principle, tannin, starch, resin, etc.

Pruni Serotinae Pulvis. (Prun. Serot. Pulv.).—Powdered Wild Cherry Bark.—Light brown powder.

OFFICIAL PREPARATION

1. **Syrupus Pruni Serotinae.** *Syn.—Syrupus Pruni Virginianae.*—**B. P. Dose.—30 to 120 ms. or 2 to 8 mils.**

ACTION AND USES.—The syrup is a sedative, because of the presence of minute quantities of hydrocyanic acid. It is used as a sweetening and flavouring agent in cough mixtures, but it can also allay cough in tea-spoonful doses, on account of its sedative virtues.

CLASS E : Drugs which disinfect the respiratory tract

Pulmonary Antiseptics

Since certain antiseptics are eliminated in the breath, it has been supposed that their internal administration should have a lethal effect on microbes in the lungs, chiefly the tubercle bacillus. For this purpose these drugs were at one time used in the treatment of pulmonary tuberculosis, and other septic conditions of the lungs. It must be borne in mind that during elimination they are considerably diluted, and do not reach the lungs in sufficient concentration to exert any destroying effect on the micro-organisms when administered *per os.* Used as an inhalation, they may have some beneficial effect in conditions characterised by offensive odour of the breath.

The pulmonary antiseptics are :

Creosote, Guaiacol, Tar Preparations, Volatile Oils, mainly Oil of Eucalyptus and Oil of Turpentine.

CREOSOTUM. (Creosot.). **Syn.**—Creasote.—Creosote is obtained by the distillation of wood tar, and contains guaiacol, creosol and other phenols.

Characters.—A colourless or yellowish, highly refractive liquid ; odour, penetrating and smoky ; taste burning. *Solubility.*—Slightly soluble in water, miscible with alcohol (90 p. c.), with solvent ether, chloroform, fixed and volatile oils.

B. P. Dose.—2 to 10 ms. or 0.12 to 0.6 mil.

GUAIACOL, B.P.C. (Not official).—Guaiacol. $C_6H_4(OCH_3)OH$.

Characters.—A colourless, oily, highly refractive liquid, or colourless crystals melting at 28° C. Odour, penetrating and smoky; taste, caustic. *Solubility.*—1 in [illegible] of water, miscible with alcohol, solvent ether, volatile and fixed oils.
Dose.—5 to 10 ms. or 0.3 to 0.6 mil.

Non-official Preparations

1. **Creosoti Carbonas.** *Syn.—Creosotal.*—**A viscid, amber-coloured almost odourless and tasteless liquid, insoluble in water, containing carbonates of guaiacol and creosol.** *Dose.*—5 to 20 ms. or 0.3 to 1.2 **mils.**
2. **Vapour Creosoti, B.P.C.**—Creosote 80 ms., light magnesium carb. 30 gr., water **q.s. 1 oz.**
3. **Syrupus Creosoti Co., B.P.C.**—Creosote 80 ms., spirit of chlorof. 1/2 oz., glycerin 3 oz. 160 ms., syrup of pine 2½ oz., syrup q.s. 10 oz. *Dose.*—60 to 120 ms. **or 4 to 8 mils.**
4. **Potassii Guaiacolsulphonas, B.P.C.** *Syn.—Thiocol.*—White powder soluble in water. Combines the good effect of creosote and guaiacol without their disadvantages. Especially useful for children. *Dose.*—8 to 15 grs. or 0.5 to 1 grm.
5. **Guaiacol Camphorate.** *Syn.—Guaiacamphol.*—A combination of guaiacol and camphoric acid. For *night sweats of phthisis. Dose.*—5 to 10 grs. or 0.3 to 0.6 grm.
6. **Guaiacol Cinnamate.** *Syn.—Styracol.*—**Insoluble in water. For** ***intestinal phthisis. Dose.*****—5 to 15 grs. or 0.3 to 1 grm.**
7. **Guaiacol Carbonas, B.P.C.** *Syn.—Duotal.*—An inodorous, tasteless powder. **Insoluble in water.** ***Dose.*****—5 to 15 grs. or 0.3 to 1 grm.**

Pharmacology of Creosote and Guaiacol

Externally.—The action of creosote and guaiacol is similar to that of carbolic acid, being **antiseptic, disinfectant** and **deodorant.** Creosote produces on the skin a sensation of burning followed by numbness and anaesthesia.

Internally. **Gastro-intestinal tract.**—In the mouth both creosote and guaiacol produce smarting and salivation, and destroy the epithelium. In the stomach they are supposed to depress the terminal filaments of the sensory nerves of the mucous membrane and to arrest putrefactive and fermentative processes by destroying low forms of vegetable life such as torulae and sarcinae without affecting the pepsin. Large doses cause nausea, vomiting, colic and diarrhoea, with frequent pulse and slow and laboured respiration.

Secretions.—They are readily absorbed into the blood, and are eliminated by the bronchial mucous membrane and kidneys, which they stimulate, increasing the bronchial and urinary secretions, and if fetid removing their foetor.

Micro-organisms.—They act as poisons to microbes, especially to tubercle bacilli when locally brought into contact with them, as by inhalation.

Therapeutics of Creosote and Guaiacol

Externally.—Creosote cannot be used as a general antiseptic on account of its indefinite composition. But as creosote vapour or creosote spray it is useful as inhalation in chronic bronchitis, phthisis, gangrene of the lungs, *etc.*

For *inhalation*, creosote may either be given alone or mixed with phenol upon a respirator, or it may be used in the form of the Vapour Creosoti, B.P.C. The Brompton for-

mula is creosote 1, spirit of menthol (20 p.c.) 1, spirit of chloroform 1.

Internally. **Gastro-intestinal tract.**—A pellet of cotton-wool soaked in creosote or guaiacol relieves toothache when introduced into the cavity of the painful carious tooth.

Lungs.—Both creosote and guaiacol were largely used in pulmonary tuberculosis, because of their supposed lethal effects on the tubercle bacilli. Commencing with 5 to 10 ms. doses either may be increased up to 30 ms. Guaiacol carbonate and thiocol are better borne than creosote. While some clinicians claim these remedies as valuable in relieving cough and expectoration and causing general improvement, others are equally sceptical and are of opinion that they are of little value. They often upset digestion when their use requires to be discontinued.

Prescribing hints.—Creosote or guaiacol may be given by mouth, in pilules, capsules, perles, emulsions or mixed with milk or cod-liver oil. Sometimes the mucus secretion of phthisis is wonderfully decreased by using the creosote spray. During haemoptysis creosote treatment must be stopped. When combined with oxide of silver it forms an explosive compound unless previously mixed with some inert powder.

CLASS F : Drugs used for X-ray examination of lungs and bronchioles

OLEUM IODISATUM

(Ol. Iodisat.)

Syn.—Lipiodol ; Iodipin.

Source.—Iodised Oil is an iodine addition product of poppy-seed oil, and may be prepared by treating poppy-seed oil with hydriodic acid. Contains 39 to 41 p. c. of combined iodine.

Characters.—A colourless or pale-yellow, clear, viscous, oily liquid ; odour, slightly aliaceous ; taste, bland and oily. On exposure to air and sunlight, it decomposes and develops a dark brown colour. Insoluble in water, soluble in solvent ether, in chloroform and in light petroleum.

ACTION AND USES

Iodised oil has been used intramuscularly as a substitute for iodides in the treatment of asthma, syphilis and rheumatic affections. It is opaque to X-rays and is used as a contrast medium to visualise bronchi and their ramifications, bronchial and pleural fistulae, permeability of bronchial fields, localisation of pulmonary cavities, and spinal cord compression. 20 to 30 mils are injected into the trachea either through a cannula introduced through the glottis or through a curved needle inserted through the crico-thyroid membrane, after anaesthetisation with cocaine. As a rule most of the drug is thrown out with the expectoration. A portion may be absorbed and excreted through the urine and saliva. When injected into the cisterna magna or into the lumbar region it helps to

localise spinal cord compression. It is non-toxic and produces no reaction when given subcutaneously or intramuscularly. It is also used to take X-ray photographs of the urethra, uterus and the fallopian tubes. It is contra-indicated in pulmonary tuberculosis as it may give rise to local and systemic reactions ; in high fever ; septic conditions and when there is intolerance to iodine.

In all cases the patient should be first tested for iodine tolerance with potassium iodide. The amount necessary varies from 5 to 40 mils (75 to 600 ms.), the average being 20 mils (300 ms.). For outlining the bronchial tree 5 to 10 mils (75 to 100 ms.) is sufficient.

GROUP IX

DRUGS ACTING ON THE GASTRO-INTESTINAL TRACT

Mouth.—Normally the mouth harbours a large number of bacteria, and although the majority of them are harmless saprophytes, under favourable conditions they are capable of developing pathogenic properties. Since many diseases arise from oral sepsis, the condition of the mouth is of great significance. Pyorrhoea alveolaris, infected tonsils and some forms of stomatitis have been known to produce diseases in some distant parts of the body. Oral sepsis is also a common cause of complication, through secondary infection, in diseases like typhoid, pneumonia, apoplexy, etc. A clean mouth therefore is of great importance in therapeutics. Unfortunately it is very difficult to keep the mouth sterile for more than a few minutes, although the use of disinfectants check the growth and further progress of the bacteria. The best means of keeping the mouth clean is by the use of dentifrices and antiseptic mouth washes so that food particles cannot lodge in between the teeth where they can undergo fermentation and decomposition. In case of septic condition of the mouth much can be done by cleaning the mouth with hydrogen peroxide, solution of iodine, either as paint or as a gargle diluted with warm water, or by the systematic use of antiseptic tooth powder. Since nearly all the microbes which commonly cause infection in the mouth are sensitive to penicillin, spraying with penicillin solution or the use of penicillin lozenges is useful.

Treatment of pyorrhoea is unsatisfactory as it is very difficult to apply any disinfectant into the infected pockets. Attempts have been made to clip off the pockets and thus prevent accumulation of pus. Application of disinfectants by ionisation has been tried apparently with good result.

Dentifrices are preparations used for cleansing the teeth. They

may be *antiseptic*, when they contain drugs like magnesium peroxide, phenol, *neem*, etc. ; and *astringent*, when they contain preparations containing tannin, like kino, krameria, myrobalans, etc.

Antiseptic mouth washes contain boric acid, phenol, thymol, potassium chlorate, etc. A useful preparation is *Liquor Antisepticus* which is an imitation of the proprietory preparation *Listerine* (*see* thymol). Hydrogen peroxide with water or solution of iodine with water may also be used (*see* Gargles, page 44).

Children often suffer from caries of the teeth, due either to acid-forming bacteria from decomposed food lodged between the teeth, or to deficiency of calcium in the system. Administration of cod-liver oil or the use of food rich in vitamin D, with plenty of milk are indicated in cases of calcium deficiency. Normally whole milk supplies sufficient calcium and vitamin D. Butter, or liquor calciferolis may also be administered to supply vitamin D.

Salivary Secretion

The saliva performs two definite functions, *viz.*—(1) Initiates the process of digestion and aids the deglutition of food ; and (2) washes out of the mouth any harmful substances. The salivary glands are supplied by (a) *sympathetic*, stimulation of which causes vaso-constriction and a scanty flow of viscid saliva ; and (b) the *parasympathetic*, stimulation of which causes vaso-dilatation and a copious flow of saliva.

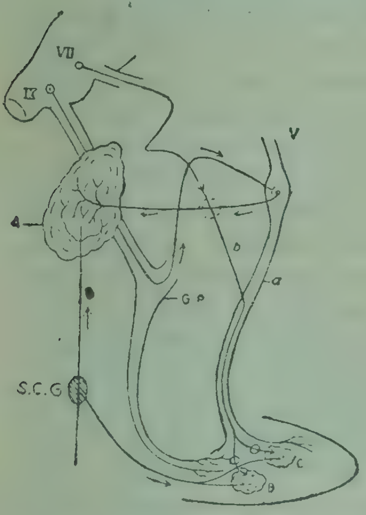


Fig. 26.—Innervation of the Salivary Glands. A, parotid : B. submaxillary ; C, sublingual glands ; s.c.g. superior cervical ganglion sending out sympathetic branches to the glands ; b, chorda tympani (parasympathetic) supplying the submaxillary and the sublingual glands through the facial. (After Meyer and Gottlieb).

Normally the secretion of saliva is increased by (*a*) the *psychic reflex*, excited by the sight or smell of food ; (*b*) the *chemical stimulation* of the nerves of taste in the mouth ; and (*c*) *mechanical stimulation* induced by chewing ; which also provokes a flow of saliva chiefly from the parotid. The amount of saliva also depends upon the condition of the water content of the blood, *e.g.* after profuse perspiration and excessive purgation the secretion is diminished and the mouth becomes dry.

Drugs which increase the secretion of saliva are called sialagogues. They may act as follows :—

1. *By exciting the periphery of the afferent nerves.*—These are acids and acid salts, pungents, aromatics, volatile oils, bitters, alcohol, ether, chloroform. They act reflexly from the mouth. Nauseants, like ipecacuanha and tartar emetic, act by stimulating the sensory ends of the vagus in the stomach.

2. *By stimulating the parasympathetic endings.*—These are

sometimes called **specific sialagogues.**—They are pilocarpine, acetylcholine, carbachol, physostigmine and muscarine.

3. *By stimulating the autonomic ganglia.*—Nicotine group first stimulate then depress.

4. *By stimulating the sympathetic endings.*—Adrenaline and ephedrine.

Many drugs, such as mercury and potassium iodide, are excreted with the saliva and increase its secretion. This is counteracted by atropine.

Drugs which decrease the secretion of saliva are called **antisialagogues.** They may act as follows :—

1. *By allaying irritation of the mouth*, as potassium chlorate, borax, astringent gargles, etc.

2. *By paralysing the parasympathetic endings.*—Atropine.

Opium and morphine also reduce salivary secretion by diminishing the excitability of the centres of secretory nerves.

Drugs Acting on the Stomach

The stomach forms the reservoir for the reception of food which it reduces to a liquid or semi-liquid condition partly by digestion and partly mechanically. The solid food remains in the stomach for several hours, and during this period the musculature contracts in such a way that the more liquid portions as they are formed are ejected at certain intervals through the pylorus into the duodenum. Except at definite intervals when the pyloric sphincter relaxes, the food is entirely shut off from the rest of the alimentary canal by the tonic contraction of both the pyloric and cardiac sphincters. The pyloric end protects the small intestine by preventing the passage of unassimilable material. This opening is under the control of reflex action and opens only when the food material has reached a certain stage of digestion. It also prevents concentrated solutions from entering the small intestine without being suitably diluted.

Two sets of nerves control the movements of the stomach, *viz.*, the *vagus* or *augmentor*, stimulation of which causes contraction, and the *sympathetic* or *inhibitor*, stimulation of which causes relaxation of the stomach and arrest of its movement, except the pyloric sphincter to which the fibres are motor. It follows therefore that all parasympathetic stimulants increase the movements of the stomach and sympathetic stimulants, like adrenaline, abolish all movements. It is essentially an autonomic organ, gastric digestion may continue both as regards secretion and movements even after section of all the extrinsic nerves.

The gastric juice performs the following functions:—*

1. *Peptic digestion.*—This is helped by the secretion of pepsin and hydrochloric acid ; and the most obvious function of the acid is to activate the pepsin to help the digestion of protein. This function however is not very important since the digestion of meat by

*Hurst, *British Medical Journal*, Oct. 13, 1934.

the tryptic ferment remains unimpaired in the absence of hydrochloric acid.

2. *Antiseptic action.*—This is more important, as an acid secretion in the stomach kills many organisms, notably *streptococci*, which may be swallowed with food or carried from the mouth with saliva and other mucous secretions from the nose and pharynx. Moreover, the dysentery, typhoid and cholera organisms are more or less killed by the gastric juice. Increased alkalinity of the contents of the small intestine, which results from the absence of hydrochloric acid in the stomach, favours the invasion of the duodenum, which is normally acid, with *Bact. coli* from the colon. The absence of hydrochloric acid therefore will favour infection of the small intestine with *streptococci* from above and with *Bact. coli* from below. These changes combined with the mechanical irritation of the mucous membrane with insufficiently broken down food will eventually lead to chronic enteritis.

3. *Haemopoiesis.*—(*a*) *Iron absorption.*—Normally the food contains sufficient iron for the maintenance of the normal percentage of haemoglobin in the blood. In case of achlorhydria there may be deficiency of food and consequently of food iron, or if there be any loss of blood, the amount of iron absorbed from food may not be sufficient to maintain iron equilibrium, and microcytic anaemia may result. But how far this is due to failure of acid in converting the food iron into more assimilable form, or the inability of the intestine to absorb iron owing to unhealthy condition, is not settled.

(*b*) *Production of haemopoietin.*—Castle has pointed out that the gastric juice contains a substance (intrinsic factor) which acts on the protein of the food (extrinsic factor) to produce a blood maturing principle essential for the maturation of the red blood corpuscles by the bone marrow, and its absence leads to Addisonian (pernicious) anaemia. The intrinsic factor which is of the nature of an enzyme has been named by Wilkinson as *haemopoietin.*

4. *Production of Neuropoietin.*—It has been shown that the gastric juice also forms another substance allied to haemopoietin which is essential for the normal nutrition of the central nervous system. It is also of the nature of an enzyme and its absence from the gastric juice leads to the degeneration of the posterior or the lateral columns of the spinal cord.

Gastric Secretion

Gastric secretion is controlled by vagus which contains the secretory fibres. Stimulation of the peripheral end of the cut vagus is followed by secretion of the gastric juice. Pawlow and his followers have shown that the stomach of a hungry dog will secrete gastric juice if he saw or smelled food, though there was no food in the stomach, and this was possible as long as the vagi were intact. It is evident that sensation of taste, odour, etc., reflexly stimulates the secretory fibres of the vagus, and the secretion so induced is termed "*psychic or appetite juice.*" Gratification of the appetite by food not only increases the gastric secretion but also the secretion of saliva. This secretion is dependent upon the presence of the motor fibres of the vagus, and section or paralysis of the vagus by atropine fails to produce the secretion. This secretion initiates gastric digestion which is supplemented by further secretion arising in the stomach itself. It has

therefore been suggested that this supplemental secretion is due to some chemical or hormonic stimulus. In fact Edkins* has shown that extracts of pyloric mucous membrane when injected into the blood cause an increased secretion of gastric juice. This has been attributed to the formation of *secretagogues* produced by some food and which acting on the pyloric mucous membrane form *gastrin* or *gastric secretin*, which being carried through the blood, acts as a chemical stimulus to the glands. Some foods, chiefly meat extracts, soup, etc., provoke the formation of this chemical stimulus, while white of egg, bread, and isotonic salt solution produce no such action.

1. **Drugs which increase gastric secretion and thus improve appetite and digestion are known as stomachics.**—They act (1) *Reflexly by stimulating the nerves of the mouth*, so-called *psychic secretion.* Substances, which stimulate the gustatory endings of the mouth in an agreeable manner and which excite sensation of appetite, increase the secretion of gastric juice. To this class belong good food, condiments and wine. Bitters and aromatics before meals stimulate psychic secretion reflexly through the nerves of taste ; (2) *by stimulating secretory fibres of the vagus*, pilocarpine, acetylcholine and muscarine ; these are not used therapeutically ; (3) *by direct stimulation of the fundus.* Pawlow has shown that alcohol in concentration of above 5 p.c. increases gastric secretion by stimulating the mucosa of the fundus; (4) *by stimulation of the pylorus*; certain meat extracts, fatty acids, soups, etc., act as chemical stimulus, probably through hormonic action; (5) *alkalies*, when given before meals increase the quantity of gastric juice.

Subcutaneous injection of histamine acid phosphate (1 mg.) increases gastric secretion in doses which have no effect on blood pressure. The secretion contains more hydrochloric acid and less pepsin. Injection of insulin (7 Units) subcutaneously is followed by an increased gastric juice resembling that produced by vagus stimulation and is rich in both hydrochloric acid and pepsin. It has been suggested that *gastrin*, and possibly also *secretin*, are probably histamine or a closely related derivative.

2. **Drugs which decrease the secretion of the gastric juice.**—Increased secretion of gastric juice or hyperchlorhydria may occur and requires treatment. The secretion is diminished by (1) *astringents*, *e.g.* salts of metals, opium, and substances containing tannin ; these reduce vascularity and act as astringents ; (2) *atropine*, which paralyses the vagus endings ; (3) *fixed oils* and *fats* ; (4) *alkalies*, these are largely used in certain forms of dyspepsia to neutralise excessive acidity due to lactic and fatty acids ; the gastric juice is at first diminished but after recuperation the glands secrete more acid ; (5) *direct action* on the fundus. Irritation first increases and then decreases gastric secretion.

Just as peripheral stimulation increases psychic secretion, so also excitement, violent emotion and anxiety inhibit this secretion. Iced water will also diminish the secretion. Drinking iced water during or just before meals is therefore not desirable for proper digestion.

Hyperchlorhydria is common in patients suffering from gastric or duodenal ulcer. These are treated by **gastric antacids.** They may act (a) by *direct neutralisation*, i.e. alkalies. Of these magnesium oxide is best as it does not form CO_2 which itself excites for-

*Journal of Physiology, 1906.

mation of gastric secretion. Calcium and magnesium carbonates come next and are stronger than bicarbonates of sodium and potassium. Bismuth carbonate is least powerful. All these are *non-buffer salts* ; (b) by *buffer substances.* These lower hydrogen-ion concentration. To this class belong magnesium trisilicate, sodium citrate and aluminium hydroxide. Magnesium trisilicate and aluminium hydroxide combine with and adsorb acid but do not produce alkalosis or affect the acid-base balance in any amounts.

Gastric antacids may be classified therapeutically into (i) *local antacids,* i.e. those whose bases are poorly absorbed and therefore produce no direct effect on the acid-base equilibrium of the blood. These are magnesium trisilicate, calcium carbonate and aluminium hydroxide; (ii) *systemic antacids.* These are freely absorbed from the gastro-intestinal tract and their absorption in large doses augments the alkaline reserve of the blood producing alkalosis. They are carbonates and bicarbonates of sodium and potassium, sodium citrate; etc.

Buffer substance is one which when present in solution maintains a constant pH when an acid or an alkali is added to it. It takes up, as it were, the shock of the strong acid or base, hence the name "buffer." Blood is a complex buffer material which keeps constantly at pH of 7.3 to 7.4. Important buffer substances of the blood are carbonate and bicarbonate of sodium, monobasic and dibasic phosphates, haemoglobin and its salts, etc.

3. **Drugs modifying gastric movements.**—Excessive movements of the stomach demand the use of drugs which have a soothing effect on the mucous membrane, or which will act through the motor mechanism. *Gastric sedatives* are drugs which soothe the mucous membrane of the stomach. They are cocaine, chlorbutol, or those which relieve vomiting (*see* antiemetics, page 355). Atropine, pethidine and adrenaline reduce excessive movements. Opium diminishes gastric movements by acting on the muscle and causes contraction of the pyloric sphincter. Insoluble salts of bismuth, magnesium and calcium form protective coating and reduce gastric movements, while cocaine, hydrocyanic acid dilute, chlorbutol and chloroform depress the sensory endings and reduce reflex movements of the stomach.

The effect of acids and alkalies on gastric movements is of some practical value. The presence of free acid in the stomach causes closure of the cardiac orifice, increases pyloric peristalsis and opens the pyloric sphincter and allows the gastric contents to enter the duodenum. The presence of free acid in the duodenum causes reflex closure of the pylorus which does not open till the contents have been neutralised by the intestinal juices. It will thus be seen that the control of the pyloric sphincter depends more upon the duodenum than on the stomach. Irritant solutions however cause closure of the pylorus, as happens when emetics are used, or when there are irritating food materials, when the stomach itself will reject by emesis, whereby the cardiac sphincter opens and the pyloric sphincter remains closed. Alkalies as a rule retard the emptying of the stomach, but the contents are emptied almost at the same rate when they are feebly alkaline or acid, or neutral.

4. **Drugs that help expulsion of gas, or carminatives.**—These act by (1) exciting regular peristaltic movements ; (2) dilating either the cardiac or sometimes the pyloric sphincters ; (3) stimulating the nerves and muscles. The volatile oils are best in this respect. Aromatics and aromatic bitters, camphor, menthol, spirits, etc., are used to expel gas from the stomach.

Class A : Vegetable bitters

The quality of bitterness is widely distributed through-

out the vegetable kingdom, but many drugs, while possessing the bitter taste, have other and more important acitons which overshadow the bitter quality, *e. g.* nux vomica on the nervous system, and quinine as antiperiodic. On the other hand, bitterness is the only quality of the drugs of this group and their therapeutic uses are linked with this property. Bitters in this sense form a class of the larger group of *stomachics.*

Bitters are divided into :—

(*a*) *simple bitters*, like calumba, quassia, gentian, chirata ; and
(*b*) *aromatic bitters*, aurantii cortex. The presence of volatile oil in this group materially adds to the stimulating effect.

CALUMBA. (Calumb.). **Syn.**—Calumbae Radix.—Calumba is the dried transversely or obliquely cut slices of the root of *Jateorhiza palmata.*

Characters.—In irregular, flattish, circular or oval, centrally depressed pieces ; 2 to 6 cm. or more in diameter, 3 to 12 mm. in thickness ; yellowish. Cork, brownish, wrinkled ; cortex, thick with radiating lines.

Composition.—(1) *Columbin*, a colourless crystalline bitter principle. (2) Three yellow crystalline alkaloids allied to berberine -*Columbamine*, *Palmatine* and *Jateorhizine*, (3) *Columbic acid*, (4) *Starch*, (5) *Mucilage.* No tannic acid.

Calumbae Pulvis. (Calumb. Pulv.). Powdered Calumba.—Yellowish grey in colour.

Official Preparations

1. **Infusum Calumbae Concentratum.**—B. P. Dose.—30 to 60 ms. or 2 to 4 mils.
2. **Infusum Calumbae Recens.**—Fresh infusion should be used within 12 hours of its preparation. B. P. Dose.—1/2 to 1 oz. or 15 to 30 mils.
3. **Infusum Calumbae.**—1/2 to 1 oz. or 15 to 30 mils.
4. **Tinctura Calumbae.**—10 p.c. B. P. Dose.—30 to 60 ms. or 2 to 4 mils.

QUASSIA. (Quass.). **Syn.**—Quassiae Lignum.—Quassia is the dried stem-wood of *Picraena excelsa*, known in commerce as Jamaica quassia.

Characters.—Logs of varying length, or in chips or raspings ; yellowish white, tough, dense, but easily split. Inodorous. Taste, intensely bitter.

Composition.—(1) *Quassin*, a mixture of *a-picrasmin* and *β-picrasmin*, bitter principle. No tannin.

Quassia Pulvis. (Quass. Pulv.).—Powdered Quassia.—Pale buff in colour.

Official Preparations

1. **Infusum Quassiae Concentratum.**—B. P. Dose.—30 to 60 ms. or 2 to 4 mils.
2. **Infusum Quassiae.**—B. P. Dose.—1/2 to 1 oz. or 15 to 30 mils.
3. **Infusum Quassiae Recens.**—B. P. Dose.—1/2 to 1 oz. or 15 to 30 mils. Should be used within 12 hours of its preparation.
4. **Tinctura Quassiae.**—10 p. c. B. P. Dose.—30 to 60 ms. or 2 to 4 mils.

GENTIANA. (Gentian.). **Syn.**—Gentianae Radix.—Gentian is the dried rhizome and root of *Gentiana lutea.*

Characters.—In yellowish-brown, entire or longitudinally split wrinkled cylindrical pieces, seldom exceeding 2½ cm. thick, varying in length, encircled by leaf-scars and terminated by a leaf-bud. Odour characteristic, Taste, first sweetish, then bitter. Should not yield *reactions with starch.*

Composition.—Contains (1) *Gentiin*, a glycoside, and (2) *Gentiamarin.* (3) *Gentisic acid.* (4) A trisaccharide. *Gentianose*, pectin and *oil.*

Incompatibles.—Iron and lead salts, silver nitrate.

Gentianae Pulvis. (Gentian. Pulv.).—Powdered Gentian.—Light brown or yellowish-brown.

Official Preparations

1. **Infusum Gentianae Compositum Concentratum.**—B. P. Dose.—30 to 60 ms or 2 to 4 mils.

2. **Infusum Gentianae Composita.** 1 in 10. B. P. **Dose.**—1/2 to 1 oz. or 15 to 30 mils.
3. **Tinctura Gentianae Composita.** 1 in 10. B. P. **Dose.**—30 to 60 ms. or 2 to 4 mils.

Chirata. I. P. L. Syn.—*Chireta*, Beng., *Chirayata*, Hind.

The dried plant, *Swertia chirata*, collected when in flower and dried.

Composition.—(1) *Chiratin*, an active amorphous bitter principle in combination with (2) *Ophelic Acid*. No tannic acid.

Dose.—10 to 30 grs. or 0.6 to 2 grms.

Preparations

1. **Infusum Chiratae Compositum Concentratum. I. P. L.**—Chirata 10, dried sweet-orange peel 10, lemon peel 20, alcohol (25 p. c.) 120. *Dose.*—30 to 60 ms. or 2 to 4 mils.
2. **Tinctura Chiratae Composita. I. P. L.**—Chirata 100 g., dried sweet-orange peel 37.5 g., cardamom 12.5 g., alcohol (45 p.c.) 1000 mils. *Dose.*—30 to 60 ms. or 2 to 4 mils.

AURANTII CORTEX RECENS. (Aurant. Cort. Rec.). **Syn.**—*Kamala Nembur Khosa*, Beng.—Fresh Bitter-Orange Peel is the fresh outer part of the pericarp of the ripe, or nearly ripe, fruit of *Citrus Aurantium*.

Characters.—Thin strips with but little of the white spongy part of the pericarp attached. Outer surface, red or deep orange-red and pitted. Epidermal cells, small and polygonal. Odour, fragrant; taste, aromatic and bitter.

Official Preparations

1. **Tinctura Aurantii.**—1 in 4. B. P. **Dose.**—30 to 60 ms. or 2 to 4 mils.
2. **Syrupus Aurantii.**—1 in 8. B. P. **Dose.**—30 to 120 ms. or 2 to 8 mils.

Aurantii Cortex Siccatus. (Aurant. Cort. Sicc.).—Dried Bitter-Orange Peel is dried outer pericarp of the ripe, or nearly ripe fruit of *Citrus Aurantium*.

Composition.—(1) A *volatile oil*, 1 to 2 p. c. which consists of a terpene, dextro-rotatory limonene. (2) Three *glucosides*; hesperidin, iso-hesperidin, aurantiamarin, a bitter principle.

Enters into.—Inf. Gent. Co., Inf. Gent. Co. Conc., Tinct. Gent. Co.

Official Preparations

1. **Infusum Aurantii Concentratum.**—B. P. **Dose.**—30 to 60 ms. or 2 to 4 mils.
2. **Infusum Aurantii.**—B. P. **Dose.**—1/2 to 1 oz. or 15 to 30 mils.

Aurantii Dulcis Cortex. I. P. L. (Aurant. Dul. Cort.).—Sweet Orange Peel is the fresh or dried outer part of the pericarp of the ripe or nearly ripe fruit of *Citrus aurantium var. sinensis*.

Preparation

1. **Aqua Aurantii Floris. I. P. L.**—It is a saturated solution of the odoriferous principles of the flowers of *Citrus aurantium*. Prepared by distilling the fresh flowers with water and separating the excess of volatile oil from the clear aqueous portion of the distillate.

Pharmacology of Bitters

Internally.—Pure bitters stimulate the nerves of taste and reflexly increase the salivary and gastric secretions. Bitters have no action on the stomach, and introduced directly into the stomach through a tube cause no increase of gastric secretion. It is the bitter taste that determines the action and by acting on the gustatory nerves they stimulate the activity of the gastric glands. As a consequence the appetite is sharpened and digestion is improved. The gastric ferments are not increased although the increase of gastric juice augments the flow of pancreatic secretion. Bitters are used as stomachics and appetisers. Their efficacy is increased by combining with aromatics and alcoholic preparations. Large doses produce opposite

effects, i.e. diminish the secretion. If continued long they derange digestion by producing gastric catarrh.

In addition to the bitter property, aromatic bitters, because of the presence of volatile oils, act as carminatives.

Blood.—Most bitters, like volatile oils, produce leucocytosis.

THERAPEUTICS OF BITTERS

Bitters are largely used to promote appetite and digestion in conditions where the stomach participates in the general enfeeblement of the functional activity caused by various diseases, overwork or starvation. They are specially valuable during the period of convalescence from acute diseases, but are contra-indicated in all diseases of the stomach that are accompanied by pain, vomiting, inflammation or ulceration, such as gastritis, gastrodynia, gastric ulcer, gastric cancer. An infusion may be injected into the rectum as an anthelmintic for thread-worms.

Prescribing hints.—Bitters should not be given in a concentrated form for a long time without interruption. Calumba is the least irritant of them all. Being free from tannin, calumba, quassia and chirata can be given with iron. They may be usefully combined with dilute hydrochloric acid; or if there is any irritability of the stomach, with alkalies and bismuth salts. They are generally used 20 to 30 minutes before food. Quassia being devoid of flavour is intensely bitter.

CLASS B: Digestive ferments

1. Proteolytic Ferments

PEPSINUM

Pepsin. (Pepsin.)

Source.—Pepsin is a proteolytic enzyme of the gastric juice of animals. Obtained from the mucous membrane of the stomach of certain animals commonly employed for food. It dissolves not less than 2500 times its weight of coagulated egg albumen.

Characters.—A [illegible], or light buff-coloured, amorphous powder, or translucent [illegible]. *Solubility.*—In water, [illegible], insoluble in alcohol (90 p.c.) and in [illegible].

B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

NON-OFFICIAL PREPARATIONS

1. **Mistura Bismuthi Composita cum Pepsino.**—[illegible] water. *Dose*—½ to 1 dr. or 2 to 4 mils.
2. **Mistura Bismuthi Composita cum Pepsino et Morphina.**—Contains 1/40 gr. of Morphine [illegible].
3. **Glycerinum Pepsini.** B. P. C.—[illegible] or 2 to 4 mils.

PHARMACOLOGY AND THERAPEUTICS

Medicinal pepsin can convert outside the body in the presence of warmth, moisture and acidity, proteins (albu-

min, fibrin, etc.) into peptones, and this action is take advantage of in predigesting food.

Internally.—A similar process within the stomach, a seen outside, takes place when pepsin is given by th mouth. It is therefore used in helping the digestion o those in whom the secretion of the gastric juice is deficien

It is recommended in diarrhoea of children, and som forms of vomiting caused by imperfect digestion. Pepsi should, however, be used with judgment, for if continue too long it may lead to gastric atrophy. In fact most case do well without any ferment. Pepsin is effective only i the presence of acid, the optimum percentage bein 0.4 p.c. The gastric juice is more often deficient in hydro chloric acid, rarely the enzyme, and administration of dilut hydrochloric acid alone will help digestion by convertin inactive pepsinogen into pepsin.

Prescribing hints.—Pepsin may be given in powders, pills, ca chets, tablets or capsules. Many of the market preparations ar worthless. Being reliable, glycerinum pepsini is the best to use. I should be given with, or directly after, meals, either with, or fol lowed by, a dose of dilute hydrochloric acid.

Peptonum, B.P.C.—Peptone is a product of digestion of bloo fibrin or other suitable proteins. Consists of a mixture of proteose peptones and amino-acids. A light yellowish-brown powder; odou faint and meat-like. Readily *soluble* in water.

Dose.—5 to 15 grs. or 0.3 to 1 grm. *By intramuscular or intra venous injection*:—1/6 to 1½ gr. or 10 to 100 mg.

USES

Peptone is used for non-specific desensitization i allergic conditions, and 0.5 grm. (7½ grs.) in cachets ha been recommended an hour before meals in urticaria an migraine of gastro-intestinal origin which are instance of anaphylaxis. It has also been used in asthma, ha fever, prurigo, eczema and angioneurotic oedema. Injec tions of peptone once a week have been attended with goo results in bronchial asthma by rendering the patient non sensitive to protein. For intravenous use a 5 p.c. solu tion in normal saline is used. Begin with 5 ms. and in crease with each dose by 2½ ms. unless or until it produce too marked a general reaction. For intramuscular injec tion a 7.5 p.c. solution is used, commencing with 0.3 mi and increasing by 0.2 mil to a maximum of 1.5 mils whic is reached at the 7th dose. These injections are give once or twice a week. Similarly, intravenous injection o peptone is useful in various forms of infective fevers (*se* Protein Therapy).

PANCREATINUM. (Pancreatin.).—Pancreatin is a prepara tion of the pancreas, containing the enzymes, trypsin, amylase, an lipase. Prepared from the fresh pancreas of certain animal commonly employed for food, by extraction of one part with fou parts of alcohol (25 p.c.).

Characters.—A colourless, or buff-coloured, amorphous powder; odour, meaty. Soluble in water, forming a slightly turbid solution; insoluble in alcohol (90 p.c.) and in solvent ether. Should be kept in well-closed containers in a cool place.
B. P. Dose. 3 to 10 grs. or 0.2 to 0.6 grm.

NON-OFFICIAL PREPARATIONS

1. **Liquor Pancreatini, B.P.C.** *Syn.—Liquor Pancreatis.*—Pancreatin 75 gr., sod. bicarb. 150 gr., glycerin 1½ oz., alcohol (90 p.c.) 1½ oz., distilled water to 10 oz. Dose—30 to 120 ms. or 2 to 8 mils.
2. **Tabellae Pancreatini Co., B.P.C.** *Syn.—Peptonising Tablets.*—Pancreatin 2½ gr., sod. bicarb. 10 gr., sucrose 2½ gr. Two tablets dissolved in 5 oz. of tepid water, are sufficient to peptonise 1 pint of milk.

PHARMACOLOGY AND THERAPEUTICS

Internally.—Pancreatin and peptonising tablets are best suited for predigesting liquid food before administration in dyspepsia, diarrhoea, and gastric troubles. Children deprived of natural nourishment fare well on pancreatised food. Pancreatin pills coated with keratin can be given two hours after meals with 20 grs. of sodium bicarbonate. Keratin protects them from the acid of the stomach. The value of pancreatic ferment is more problematical than that of pepsin. Pancreatic emulsion is often given with cod-liver oil in wasting diseases when the stomach cannot well digest fat.

Papainum, I. P. L. (Papain.).—Papain is a proteolytic enzyme, or a mixture of several enzymes obtained by adding alcohol to the freshly drawn juice of the unripe fruit or other parts of *Carica papaya.*

Dose.—2 to 10 grs. or 0.12 to 0.6 grm.

NON-OFFICIAL PREPARATION

1. **Glycerinum Papaini, I.P.L.**—Papain 11 G., dilute hydrochloric acid 8 ml., simple elixir 5 ml., glycerin q. s. 100 mil. *Dose.*—30 to 60 ms. or 2 to 4 mils.

USES.—Papain is a proteolytic enzyme or a mixture of several enzymes, and is used for the same purposes as pepsin. It is also useful as an anthelmintic for ascarides. The dry powder may be used, or it may be administered in the form of glycerin.

2. Amylolytic Ferments

EXTRACTUM MALTI. (Ext. Malt.).—Extract of Malt is prepared from sound, malted grain of barley, *Hordeum distichon*, or a mixture of this with not more than 33.0 p.c. of sound malted grain of wheat, *Triticum sativum*. Contains nitrogen equivalent to not less than 4.0 p.c. w/w of protein.

Characters.—An amber or yellowish-brown, viscous liquid; odour, agreeable and characteristic; taste, sweet. Miscible with water in all proportions, forming a translucent solution.
B. P. Dose.—60 ms. to 1 oz. or 4 to 30 mils in divided doses, daily.

OFFICIAL PREPARATION

1. **Extractum Malti cum Oleo Morrhuae.**—Approximately 15 p. c. v/v cod-liver oil or 72 ms. in 1 oz. **B. P. Dose.—60 ms. to 1 oz.** or 4 to 30 mils in divided doses, daily.

PHARMACOLOGY AND THERAPEUTICS

The various malt extracts are valuable as foods for persons suffering from *wasting diseases*, such as phthisis, as they are easily tolerated by the stomach, and maltose

leads to the formation of fat. Being sweet they may used either alone or combined with cod-liver oil. Malt a good source of vitamin B. Powdered malt in combin tion with baked wheaten flour in varying proportio forms most of the popular infant's foods. It may also taken mixed with milk or beer or sprinkled over porrid but as diastase only acts in an alkaline medium it is be to give malt two hours after a meal. It is doubtful if exerts any appreciable effect in promoting carbohydra digestion.

TAKA DIASTASE. (*Not official*).—An enzyme obtained fr a species of *Eurotium oryzae*, cultivated on bran. A yellowish-wh powder, which changes in a few minutes a hundred times its weig of starch into maltose.

Dose.—1 to 5 grs. or 0.06 to 0.3 grm.

USES.—It is very valuable in all forms of starchy dyspeps with hyperacidity such as are common amongst the rice-eating habitants of Bengal, and it will be found *preferable to pepsin in cases of this kind*. It may be combined with sodium bicarbonate.

CLASS C : Emetics

Vomiting is a complex physiological phenomenon produce which several parts are brought into play. T chief of them is the vomiting centre in the medulla a the afferent stimuli carried to the centre from vario sources. The centre may be excited *directly* by distur ances in the cerebral circulation (anaemia of the brain or by mechanical and chemical stimuli, *e.g.* pressure d to growth, meningitis, uraemia, etc. ; or *indirectly* certain peripheral stimuli, *e.g.* various unpleasant sens tions, repulsive sight, offensive smell, acute pain (re colic), disturbances of the labyrinth (sea-sickness), a by certain drugs and poisons.

Emetics are drugs which produce vomiting. This often accompanied by nausea, salivation, sweat, secreti of mucus from the air passages and oesophagus, qui pulse and irregular respiration. During the act of vom ing the cardiac sphincter opens and the pyloric porti of the stomach tightly contracts, and the contents of t stomach are expelled by a simultaneous contraction the abdominal muscles and the diaphragm. The ordination of all these movements is controlled by t vomiting centre. Emetics are classified as follows :—

(1) *Local or Reflex Emetics*, also called *Gastric Emetics* These cause vomiting by irritating the sensory endings of the va in the stomach. They act only when they reach the pyloric end of stomach, and therefore act better when used with a large bulk water for rapid action, as they then reach the pyloric end rapi They are used in cases of poisoning, but being irritants they h an injurious effect if emesis does not occur. Lavage of the stom in poisoning is more preferred than the use of local emetics. gastric irritants act as emetics. Thus vomiting is a comm

accompaniment of almost all irritant poisons. The emetics are : zinc sulphate, alum, ipecacuanha, emetine, bicarbonate of ammonia, copper sulphate, tartar emetic, mustard, common salt, warm water. When vomiting is due to irritation of the stomach it is best treated by removal of the irritant.

(2) *Central Emetics.*—These act by stimulating the vomiting centre after absorption. As apomorphine.

Digitalis, morphine and lobeline also cause vomiting by stimulating the centre.

Therapeutics.—Emetics are used (1) to remove foreign bodies from the throat and oesophagus ; (2) to expel undigested substances and poisons from the stomach ; and (3) to increase secretion of bronchial glands in small doses.

They are *contra-indicated* in hernia, aneurism, severe heart disease, prolapse of the rectum and uterus, peritoneal and intestinal inflammation, and in cases of threatened abortion, or when there is tendency to haemorrhage or atheroma of vessels, and in debilitated conditions for fear of collapse.

CLASS D : Antiemetics

These are drugs which are used to stop vomiting. They may act locally, when they are called *direct antiemetics*, or centrally. Examples of central vomiting are sea-sickness, air-sickness, vomiting of pregnancy, cyclic vomiting and vomiting due to passage of calculus through the ureter or bile duct. Prevention of central vomiting is rather difficult; drugs which depress the vomiting centre are generally effective. Barbiturates, bromides and chloral hydrate are largely used; hyoscine is useful in sea-sickness and air-sickness. Atropine counteracts the vomiting due to morphine and pyloric spasm. Common antiemetics are: small doses of adrenaline solution, carminatives like brandy, champagne, chloroform water, bicarbonate of sodium and other antacids; drop doses of ipecacuanha tincture; local sedatives like dilute hydrocyanic acid, cocaine, chlorbutol, ice and hot water ; fractional doses of calomel : mustard application to the epigastrium. Bismuth and kaolin stop vomiting by forming a protective coating over the mucous membrane of the stomach. Pyridoxine hydrochloride has been found useful in radiation sickness and vomiting of pregnancy.

ACIDUM HYDROCYANICUM DILUTUM, B.P.C. (Acid. Hydrocyan. Dil.). HCN. Syn.—Diluted Hydrogen Cyanide ; Dilute Prussic Acid.

Characters.—A colourless, volatile liquid with characteristic odour ; faintly acid. **Dose.—2 to 5 ms. or 0.12 to 0.3 mil.**

PHARMACOLOGY

Externally.—Hydrocyanic acid is a protoplasmic poison and is absorbed from the epidermis, but more readily from a raw surface. It paralyses the sensory nerve endings and thus acts as a local sedative and anaesthetic.

Internally. **Alimentary canal.**—It has an acrid bitter taste and causes burning and reflexly salivation followed by numbness in the mouth and throat. It is absorbed rapidly by the mucous membrane,

depresses the sensory nerve terminations and acts as a gastric sedative.

Blood.—It quickly enters the blood from all parts of the body and in poisoning it causes paralysis of the intracellular catalase ferment and prevents the cells from utilising the oxygen from the blood; consequently the oxyhaemoglobin is not reduced in the capillaries, so that the venous blood is found scarlet red and the tissues suffer from oxygen starvation. If however death is delayed or the dose is not lethal, the acid is rapidly changed to harmless products in the tissues, which enable the protoplasm to recover its oxygen-absorbing power; the expired air becomes less rich in oxygen and contains more carbon dioxide and the venous blood regains its usual dark purple colour.

Heart and blood-vessels.—A small dose stimulates the vagal centre and slows the pulse. A large dose at once arrests the heart in diastole due to direct action on the cardiac centre, and on the heart. The blood pressure is first momentarily heightened and afterwards deeply lowered from a transitory stimulation and subsequent paralysis of the vaso-motor centre.

Respiration.—It is excreted by the bronchial mucous membrane and depresses the sensory endings thus acting as a sedative and reduces cough. A small dose makes the respiration quicker and deeper, but this is soon followed by depression when respiration becomes feeble and laboured and death takes place from paralysis of the centre, except in those cases where the heart is instantly stopped by a large dose.

Nervous system.—Small doses stimulate and large doses depress the vagal, vaso-constrictor and respiratory centres. The reflex excitability of the cord is first lowered and then abolished altogether. The peripheral sensory nerves are less affected by internal administration than by local application. The motor nerves and muscles are also paralysed.

Acute toxic action.—Because of its quick action it is often employed for suicidal purpose. Poisoning also may occur from inhalation of the gas used in fumigation. If the dose be large, it is followed almost instantaneously by a gasping cry, a few convulsive movements and death. But with a smaller dose, the patient becomes unconscious; his eyes fixed; pupils, dilated; pulse, feeble and irregular or imperceptible; respiration, slow, deep and convulsive with frothing at the mouth; skin, cold and clammy and at last death occurs.

Treatment.—Because of its rapid action treatment of cyanide poisoning is very limited. Whenever possible attempt should be made to evacuate the poison or to destroy the poison in the stomach. Animal charcoal, hydrogen peroxide, permanganate of potassium (1 in 1000), or sodium thiosulphate 5 p.c. should be given promptly followed by lavage with one of these solutions diluted 1 in 10. Artificial respiration or 5 p.c. CO_2 with oxygen. Fall of pressure should be treated with adrenaline. Sodium nitrite 1 p.c. solution should be injected in 10 mils doses intravenously up to 50 mils in an hour alternating with sodium thiosulphate 5 p. c. in isotonic (1.8 p.c.) sodium sulphate solution, 50 mils at a time up to 500 mils if necessary. For cyanosis transfusion of blood.

Fatal Dose.—1 gr. or 60 mg. of pure HCN; 3 to 5 grs. or 0.2 to 0.3 grm. of KCN.

THERAPEUTICS

Externally.—Dilute hydrocyanic acid is rarely used now. It removes the itching of urticaria, lichen and dry eczema, when the affected parts are bathed or sponged with a lotion (2 drs. to 8 oz. of rose water and glycerin). Care should be taken not to apply the lotion to a raw surface.

Internally.—For irritative gastric disorders and dyspepsia it is ordinarily prescribed with sodium bicarbonate and bismuth carbonate as a gastric sedative. It is also used to stop vomiting of dyspepsia, gastric ulcer and of pregnancy in 1 to 2 ms. doses and to relieve the hacking cough of phthisis, and the spasms of hiccough. For this purpose it is generally used either in the form of syrup of wild cherry (*see* page 342), or tinct. chloroformi et morphinae co.

Class E : Adsorbents

Charcoal, Kaolin (*see* **page 129**), **Magnesium Trisilicate** (*see* page 105), **Aluminium Hydroxide** (*see* page 128).

Carbo Ligni Activatus, I. P. L.—Activated Wood Charcoal is the residue from the destructive distillation of vegetable matter such as saw-dust, cellulose residues and coconut shells treated to increase its adsorptive power.

Characters.—Fine, black, odourless, tasteless powder, free from gritty matter.
Dose.—60 to 240 grs. or 4 to 16 grms.

Pharmacology and Therapeutics

When gases or substances in solution get fixed on the surface of a solid, they are said to be *adsorbed.* Adsorbents are used in medicine to remove undesirable substances like toxins or poisonous gases in the intestine. Adsorption is a purely physical process, although the adsorbed substance may form a chemical compound with the molecules on the surface of the adsorbent. To be useful the substance must have a large surface compared with its volume and that the surface should be clean.

If we dissolve a dye in distilled water and pass it through finely powdered charcoal we find that most of the colour disappears. No chemical reaction has taken place, but the powdered charcoal has a large surface, and the action of this upon the dissolved particles of dye has made these accumulate or condense upon the surface of the charcoal by process of adsorption. This property is taken advantage of in the therapeutic uses of charcoal.

Externally.—Dry charcoal adsorbs and condenses gases within its interstices, specially oxygen, which it parts with to oxidise organic and other substances either liquid or gaseous. Hence it acts as a **disinfectant** and **deodorant.** It may, by giving off oxygen, help the growth of anaerobic organisms. In the same manner it adsorbs colloidal impurities, proteins, etc. The process of adsorption, being a surface action, is a purely physical phenomenon and the effect is greatest when the surface is very large, *i.e.* the particles are very small, or the surface has been made greater by porosity.

Internally.—It exerts the same adsorptive power in the stomach and intestine and therefore it is used in cases of poisoning by phosphorus, alkaloids, etc., and as it prevents the absorption of the poison, its use should be followed by an aperient, preferably a saline, to expel the contents. Alone or combined with kaolin, which also acts in the same way, it is used in **diarrhoea, dysentery** and **cholera,** where it acts by checking bacterial growth and by adsorption of irritating putrefactive products.

Activated charcoal may be used in powder, cachets or lozenges, either alone or combined with kaolin, bismuth carbonate and betanaphthol in the treatment of flatulence and acid dyspepsia.

Drugs Acting on the Intestine

We have already seen that the acid chyme from the stomach enters the duodenum in driblets and Mellanby has shown that the presence of this liberates a hormone which excites the contraction of the gall-bladder so that a certain

amount of bile enters the duodenum. The bile acids and their products of decomposition are partly absorbed and help the formation of secretin which stimulates both the pancreatic secretion and bile. Therefore the chyme is subjected to a further process of digestion by the secretions from the liver, the pancreas and the intestinal glands. The chyle and other soluble ingredients are absorbed by the lacteals and the portal veins as the chyme is propelled downwards by the intestinal movements.

Four kinds of movements, *viz., pendulum, rhythmic segmentation, peristaltic* and *vermiform,* occur in the intestine. The pendulum movements consist of rhythmic contraction and relaxation and is due to the spontaneous rhythmic action of the longitudinal muscle and takes place even in the isolated pieces of the gut. They move the contents backwards and forwards. Rhythmic segmentation helps to soften and mix the contents. It is essentially a series of local contraction of the circular muscle and occurs at those portions where the food mass is lodged, and is possibly due to local distension caused by the food. The peristaltic movements occur every three or four minutes and pass down the intestine carrying the contents downwards. This is controlled by Auerbach's plexus which causes the circular muscles to relax below the food material and contract above it so as to force its contents downwards. They are excited reflexly by stretching and chemical stimuli. The vermiform movements are irregular and are confined to the colon.

Absorption is carried on by osmosis and diffusion, and excretion partly by osmosis and partly by the glands, which furnish the succus entericus. The excretion particularly of the watery portion is so profuse, that the effect of absorption is neutralised, and the contents of the small in-intestine and the duodenum remain liquid. In addition to this, certain micro-organisms, whose normal habitat is the intestinal tract, play an important part in the intestinal digestion. They may occasionally give rise to toxins and so produce symptoms of considerable gravity.

The absorption from the gut varies. Substances not soluble in water and lipoids are not absorbed at all, while the soluble ones are usually absorbed, though the lipoid-soluble substances more easily than the water-soluble ones. Absorption takes place from the small intestine, and the rate of absorption of water-soluble substances depends upon the rate of diffusion, which in its turn depends on the size of the molecules. True colloids, like proteins and starch, are not absorbed, but soaps and alkaloids which are semi-colloids are rapidly absorbed.

The colon has a lower absorptive power than the small intestine. Sugar and salts are absorbed from the

colon. Drugs that are absorbed by the intestine are as a rule absorbed when given per rectum, but more slowly. But substances which depend for their absorption upon the changes produced by the digestive juices are not absorbed when given per rectum. Many drugs however act quickly and strongly when administered per rectum.

The muscular coat of the gut is supplied by the sympathetic system through the splanchnic nerves, the stimulation of which causes inhibition and therefore arrest of movements, except the ileo-caecal and the internal anal sphincters, and the muscularis mucosae, to which the fibres are motor. The vagus (parasympathetic) supplies the motor or augmentor nerves, the stimulation of which increases the tone of the intestine and renders the movements more active but relaxes the sphincters. The peristalsis is essentially independent of extrinsic nervous influences. The Auerbach's plexus (which lies between the circular and longitudinal muscular coat) acts as the excitor neurone of the vagus in the intestine. The vagus supplies the motor nerve to the whole of the small intestine and part of the colon, and the pelvic nerve supplies motor fibres to most of the colon and the rectum.

Intestinal Movements.—The intestinal movements are influenced by many drugs through the nervous mechanism, or through irritation of the mucous membrane, *e. g.* irritant purgatives.

1. *The movements are increased by* (1) parasympathetic stimulation, *e. g.* by pilocarpine, physostigmine, neostigmine, carbachol and acetylcholine. These act through the vagus endings independently of the Auerbach's plexus and the sympathetic apparatus. Choline being normally present in many tissues, it is generally believed that it assists in maintaining the activity of the gut. (2) Acting directly on the muscle, as pituitary extract, lead and barium salts and histamine. Strychnine acts on the muscle and by stimulating reflex excitability of the Auerbach's plexus.

2. *The movements are diminished by* (1) nicotine, which stimulates the sympathetic ganglia ; (2) adrenaline and ephedrine, by stimulating the sympathetic endings ; (3) atropine and hyoscine, by depressing the vagus (parasympathetic) ; (4) papaverine, benzyl benzoate, pethidine, nitrites, volatile oils and chloroform, by acting locally on the muscles ; and (5) bismuth salts, calcium and kaolin, by acting as mechanical protectives. These are known as *intestinal antispasmodics.*

Violent and irregular intestinal movements occur in colic and are relieved by belladonna, opium and pethidine. Belladonna is often combined with purgatives to check irregular movements of the gut and griping. The movements are inhibited by anaesthetics or reflexly through the sympathetic. Any interference with the peritoneal cavity is followed by inhibition, as for instance post-operative paralysis of the intestine after abdominal operation. In intestinal paresis pituitary extract, neostigmine, carbachol and physostigmine are used.

Intestinal Antiseptics.—Since in most bacterial infections of the intestine the colon and the lower part of the small intestine are involved, intestinal disinfection implies disinfection of these parts. The seat of infection may be in the bowel wall itself, or the septic process may occur in the contents of the intestine. In either case

the results have been disappointing and a drug strong enough to produce any bactericidal effect has injurious action on the tissues of the gut, or may be absorbed producing toxic effects. To be of any use intestinal disinfectants should possess the following qualities:—(1) should be relatively non-toxic even if absorbed; (2) should act in an alkaline medium and in the presence of organic matter; (3) should not be destroyed in the stomach and upper part of the intestine and should have no injurious effect on the intestinal mucous membrane; and (4) should not interfere with the normal bacterial action of the intestinal mucosa. Such an ideal antiseptic is difficult to obtain and the so-called antiseptics have no such effect. In fact Schutz has shown that the healthy intestinal mucosa, which normally possesses germicidal action like other mucous membrane, becomes devoid of this property by the use of antiseptics and purgatives. Intestinal disinfection therefore is very difficult to produce, and it has been found almost impossible to cause even a diminution of the bacterial growth with certainty. Being slightly soluble, salol has often been used, which spilts into phenol and salicylic acid in the gut, but these are rapidly absorbed and may not reach the colon where disinfection is necessary, and in large doses may produce phenol poisoning. Salicylic acid, menthol, naphthol and thymol have been found effective experimentally. Fatty acid ester of thymol has been found effective in certain infections. Calomel is largely used as intestinal antiseptic; it acts not by any bactericidal action but by expelling the putrefying contents of the gut. Drugs which adsorb bacteria and toxins are sometimes more useful than many of the reputed intestinal disinfectants. Thus kaolin, which forms a coating on the whole of the intestinal mucosa, is used in the treatment of cholera and by its adsorbent effect prevents absorption of toxins. Other adsorbents are aluminium hydroxide, activated charcoal and magnesium trisilicate. By irrigation of the colon with antiseptics (permanganate of potash, silver nitrate, albargin) some disinfection can be produced locally.

Quite recently however some advance has been made in this quest and several preparations have been introduced for the purpose. One is sulphaguanidine, primarily introduced for the treatment of bacillary dysentery, but has also been used to reduce the bacterial population of the lower bowel. Other compounds of this group are succinylsulphathaizole and sulphathalidine. These are very little absorbed from the intestinal canal, only 5 p.c. being detected in the urine, therefore surprisingly large doses can be given by the mouth without any untoward general effects.

GROUP X

PURGATIVES

Purgatives, Cathartics, Evacuants, or Aperients are drugs which cause evacuation of the bowels. The act of defaecation is accompanied by increased peristaltic contraction of the rectum and opening of the internal sphincter of the anus. It is not possible to definitely ascertain what normal impulse in the rectum produces the initial reflex for defaecation, possibly a certain amount of fullness and consistency of the contents form the necessary stimulus. Purgatives act either (*a*) by increasing the volume of the non-absorbable material; (*b*) by preventing the absorption of water; (*c*) by irritating the

small and large intestine, and thus reflexly increasing peristalsis ; and (*d*) by stimulating the neuro-muscular mechanism directly. The contents of the small intestine are poured out through the ileo-caecal valve in an almost fluid condition, and the formation of the faecal masses takes place during their long stay in the large intestine. A drug, therefore, which would simply increase the peristaltic movements of the intestine may give rise to watery evacuation by hurrying the contents into the rectum without giving time for absorption of the fluid ; on the other hand the accumulation of a large quantity of fluid in the intestine reflexly excites peristalsis.

Many drugs cause looseness of the bowels, but since they act as powerful irritants they are not used as purgatives. An ideal purgative should not have any other effect except on the intestines, it should not irritate the stomach, but should become active only when it reaches the intestine. It should not be easily absorbed or absorbed so slowly that it can exert its effects throughout the intestine.

Some purgatives act mechanically, due to their bulk, and distending the bowel reflexly induce the need of evacuation. They are harmless and non-irritant and may be continued for a long time without any disadvantage. They are useful in habitual constipation and in cases where there is deficiency of sufficient ballast to form the faecal mass. Chief of these are agar-agar and cereals. While others act as mechanical lubricants. These are liquid paraffin and vegetable oils, like olive oil, in so far as they escape saponification. These substances are not irritating nor increase peristalsis, though may make normal intestinal movements more effective. Purgation is due to softening of the faecal mass.

Purgative oils, like castor oil, become active only when the fatty acids are liberated ; the anthracene purgatives act after the glycosidal compounds are split up ; while the resinous purgatives after the resins are decomposed and dissolved by alkalies and bile. Bile therefore is necessary for most resinous purgatives like podophyllum, ipomoea, jalap, etc.

Different purgatives act on different parts of the intestine. Castor oil, for instance, acts on the small intestine, having little or no effect on the colon, although Hurst has shown that in man it stimulates both the small and large intestines. Aloes, senna and other anthracene purgatives act entirely on the large intestine without producing any effect on the movements of the small intestine. They, therefore, take longer time to act. The drastic purgatives increase the peristalsis of both the large and small intestines, and in large doses cause accumulation of fluid

within the intestine. Magnesium sulphate hastens the passage through the small intestine and prevents the absorption and helps concentration of the contents in the large intestine. Calomel stimulates the peristalsis of both the small and large intestines.

Atony of the muscles of the intestine follows the use of most purgatives with consequent after-constipation. This effect is more marked after castor oil and rhubarb.

Some purgatives cause evacuation when given subcutaneously. Senna, aloes and colocynth belong to this group. But these effects are not due to any specific action on the bowel but in all probability result from their excretion into the intestine. Others again, not ordinarily used as purgatives, act as such when given subcutaneously by their special selective affinity on the nervous system and muscle. To this class belong pilocarpine, acetylcholine, neostigmine, carbachol and physostigmine which act by stimulating the vagus endings; apocodeine ($\frac{1}{2}$ gr.) and ergotamine ($\frac{1}{80}$ gr.) by depressing ends of the splanchnic or inhibitory nerves. Pituitary extract acts on the muscle directly and increases the rate and amplitude of the intestinal movements but does not augment the tone much.

Therapeutics.—The purgatives are used (1) to remove faecal accumulation in cases of constipation; (2) to drain fluid from the tissues in cases of cardiac, renal and hepatic dropsies; (3) to lower the temperature in fevers; (4) to lower the blood pressure in apoplexy and cerebral congestion; (5) to remove from the blood certain excrementitious matters; and (6) to remove irritating or otherwise harmful substances from the intestine as in food poisoning, intestinal putrefaction, and in diarrhoea due to undigested food material.

Contra-indications.—Purgatives should not be used at all or used with caution in

1. Inflammatory conditions of the abdominal organs, peritonitis, enteritis, etc.
2. During pregnancy and menstruation, when strong purgatives should be avoided.
3. Intestinal haemorrhage, prostration and collapse.
4. Intestinal obstruction and intussusception.

The purgative are classified as follows :—

Class A : Those acting by increasing the volume of non-absorbable material in the intestine.

1. Saline purgatives : these act by interfering with absorption
   Sulphate and Phosphate of Sodium, Acid Tartrate of Potassium, Sodium Potassium Tartrate, Sulphate, Carbonate and Oxide of Magnesium.
2. Laxatives : **Whole Meal Bread, Fruits, Oat Meal, Agar, Isuphgul** (q.v.), **Bael** (q.v.)

Class B : **Those acting as lubricants**
Liquid Paraffin, Olive Oil

Class C : **Those acting as irritants**

1. Mild purgatives : Castor Oil, Phenolphthalein, Sulphur (q.v.)
2. **Anthracene purgatives : Aloes, Rhubarb, Senna, Cascara**
3. Drastic purgatives : **Ipomoea, Jalap, Croton Oil, Colocynth, Kaladana** (q.v.), **Turpeth** (q.v.).
4. Cholagogue purgatives : These do not act by increasing the secretion of bile but increase its excretion by hurrying the contents of the intestine by **increasing peristalsis and thus preventing reabsorption. They are Podophyllum, Euonymus, Mercurials.**

[illegible] Hypodermic purgatives.
These drugs when administered hypodermically stimulate the motor nerves or the muscle of the intestine. They are not ordinarily used as purgatives but are useful in preventing post-operative paralysis of the gut. Pilocarpine, Physostigmine, Carbachol and Neostigmine, increase intestinal movements by stimulating the parasympathetic nerve endings; Posterior Pituitary stimulates the muscle directly.

1. Saline Purgatives

POTASSII TARTRAS ACIDUS. (Pot. Tart. Acid.). $KC_4H_5O_6$.
Syn.—Purified Cream of Tartar; Potassium Bitartrate.—Potassium Acid Tartrate may be prepared by the purification of the deposit obtained during the fermentation of grape juice.

Characters.—In gritty, white crystalline powder, or colourless, slightly opaque crystals. Taste, pleasant and acid. *Solubility*—1 in 220 of water.
B. P. Dose.—15 to 60 grs. or 1 to 4 grms.

Non-official Preparation

1. **Potus Imperialis. B. P. C.** *Syn.—Imperial Drink.*—Acid pot. tartrate 40 grs., citric acid 7 grs., sucrose 1 oz., oil of lemon 3 ms., tinct. of lemon 30 ms., water q.s. 20 ozs.

SODII ET POTASSII TARTRAS. (Sod. et Pot. Tart.).—$KNaC_4H_4O_6,4H_2O$. **Syn.**—Soda Tartarata; Rochelle Salt; Seignett's Salt.—Sodium Potassium Tartrate is obtained by neutralising acid potassium tartrate with sodium carbonate.

Characters.—Colourless crystals, or a white crystalline powder; taste, saline and cooling. *Soluble* in 1.5 parts of water, forming a clear colourless solution; almost insoluble in alcohol (90 p.c.).
B. P. Dose.—120 to 240 grs. or 8 to 16 grms.

Official Preparation

1. **Pulvis Effervescens Compositus.** *Syn.—Pulvis Sodae Tartaratae Effervescens; Seidlitz Powder.* **B. P. Dose.**—Dissolve No. 1 powder in a tumbler of cold or warm water; add No. 2 powder. To be taken while effervescing.

SODII SULPHAS. (Sod. Sulph.) $Na_2SO_4,10H_2O$. **Syn.**—Glauber's Salt.—Sodium Sulphate may be obtained by the interaction of sodium chloride and sulphuric acid.

Characters.—In colourless, odourless, crystals; taste, bitter and saline. Effloresces in dry air. *Soluble* in 3 parts of water, insoluble in alcohol (90 p. c.).
B. P. Dose.—30 to 240 grs. or 2 to 16 grms.

Sodii Sulphas Exsiccatus. **Syn.**—Exsiccated Glauber's Salt; Anhydrous Sodium Sulphate.—Exsiccated Sodium Sulphate is prepared by drying sodium sulphate at 100°C. until it ceases to lose weight. In white hygroscopic powder; odourless; taste, bitter and saline. *Soluble* in 8 parts of water.
B. P. Dose.—15 to 120 grs. or 1 to 8 grms.

SODII PHOSPHAS. (Sod. Phosph.). $Na_2HPO_4,12H_2O$. **Syn.**—Disodium Hydrogen Phosphate; Tasteless Purging Salt.—Sodium Phosphate contains not less than 99 p. c. of pure di-sodium hydrogen phosphate.

Characters.—Colourless, efflorescent, crystals. Taste, saline. Efflorescent in dry air. *Soluble* in 7 parts of cold water.
B. P. Dose.—30 to 240 grs. or 2 to 16 grms.
Enters into.—Syr. Ferr. Phosph. Co.

Sodii Phosphas Exsiccatus. **Syn.**—Anhydrous Sodium Phosphate.—Exsiccated Sodium Phosphate may be prepared by allowing sodium phosphate to effloresce for several days in warm air at a moderate temperature, followed by drying at 100°C. until it ceases to lose weight.

Characters.—A white, hygroscopic powder; odourless; taste, saline.
B. P. Dose.—10 to 75 grs. or 0.6 to 5 grms.

SODII PHOSPHAS ACIDUS. (Sod. Phosph. Acid.). $NaH_2PO_4,2H_2O$. **Syn.**—Sodium Di-hydrogen Phosphate; Sodii Biphosphas,

U. S. P.—Acid Sodium Phosphate. Contains not less than 98 p.c. of pure sodium di-hydrogen phosphate.

Characters.—Colourless crystals, or a crystalline powder; odourless; taste, acid and saline. *Soluble* in about 1 part of water.
B. P. Dose.—30 to 60 grs. or 2 to 4 grms.

MAGNESII SULPHAS. (Mag. Sulph.). **Syn.**—Epsom Salts.

Characters.—See page 104.
B. P. Dose.—30 to 240 grs. or 2 to 16 grms.

Magnesii Sulphas Exsiccatus. **Syn.**—Dried Epsom Salts.
Characters.—See page 105.
B. P. Dose.—30 to 180 grs. or 2 to 12 grms.

Pharmacology of Saline Purgatives

These salts because of their low absorbability from the gut disturb the osmotic balance between the bowel contents and the surrounding tissues. It has been found that certain salts are absorbed readily through the intestinal tract, and this depends upon the nature of the ions of which they are composed. Among those that are absorbed very slowly are the cations, calcium, magnesium, and the heavy metals; and the anions, phosphates, sulphates, tartrates, citrates, etc. Of these magnesium among the basic, and citrates, phosphates, tartrates and sulphates among the acid ions have cathartic properties. When both ions are slowly absorbed the effect is more powerful, *e. g.* magnesium sulphate is a stronger purgative than sodium sulphate, because the sodium ion is more easily absorbed than the magnesium ion, sulphate ion being common in both the salts. As a rule salines do not irritate the gut like the vegetable purgatives unless given in large doses. The action of saline purgatives is due not to irritation but to retarded absorption.

Solutions of these salts have an unpleasant salt taste, and when used in a concentrated form, they irritate the stomach and may produce nausea. If they remain longer they promote transudation and secretion and therefore help their own dilution. By means of a caecal fistula it has been shown that if an isotonic sodium chloride solution and a solution of sodium sulphate be administered by the mouth, little or none of the former reaches the caecum, while most of the latter solution escapes by the fistula, only about 10 to 20 p.c. being absorbed by the stomach and intestine above the fistula. It is evident therefore that if any of the cathartic salts be used, from 80 to 90 p.c. of the fluid reaches the large intestine where it remains unabsorbed. The catharsis is due to the large bulk of the fluid which distends the bowel and which induces increased peristalsis. The intensity of action of these salts depends upon the concentration of the solution in which they are administered. For instance, if the salt is freely diluted more of the fluid is absorbed and less reaches the large intestine. Whereas if the solution be hypertonic it will

draw fluid from the blood into the intestine, due to its higher osmotic pressure, and the blood gives up its fluid without any sufficient compensation of salt until the solution becomes isotonic. A large amount of fluid thus accumulates with the resultant evacuation. Boas on the other hand asserts that the catharsis is less powerful when the solution used is more concentrated, and that the salt is more prone to be absorbed and to produce systemic effects. He reports several cases of poisoning from concentrated doses of magnesium sulphate. It must be borne in mind that purgation is produced only if the intestine is able to furnish a sufficiently large amount of fluid, which depends upon the amount of water present in the blood and tissues. It takes a longer time to produce purgation if a hypertonic solution is used, as its entrance into the duodenum causes closure of the pylorus, and the dilution results practically only from gradual secretion of the digestive juices unless some water is taken at the same time. It may therefore take many hours before the quantity becomes large enough to produce an evacuation. A dilute solution on the other hand may cause liquid stool, provided a large amount of it rapidly passes into the large bowel. If however there be no evacuation, the salt is absorbed into the blood and excreted by the kidneys and acts as a diuretic. MacCallum has suggested that salines act by precipitating calcium in the tissues and so neutralise its depressing action. The stool generally consists of (1) the salt and the fluid derived by transudation, and (2) some of the unabsorbed gastro-intestinal contents.

Bayliss and Starling have shown that the passage of liquids along the intestine is different from that of solid or pasty matter. Whereas solids stimulate peristalsis, liquids simply generate rhythmic intestinal segmentations ; the result being that while the liquids pass along, more or less of the solid contents of the intestine are liable to be left behind. Hay has shown that when sulphate of magnesium is used for a long time it is excreted as sulphate in the urine in combination with sodium and potassium, thus reducing the alkali reserve of the body.

Therapeutics of Saline Purgatives

The saline purgatives are extensively used in cases of constipation, chiefly habitual constipation, as by increasing the fluidity of the intestinal contents they facilitate the expulsion of hard and dry faeces. They are however of little use in spastic constipation. They are taken freely diluted in warm water, first thing in the morning, or the sulphate or the tartrate may be taken in the effervescing form. Sodium sulphate is the active ingredient of many natural mineral waters, *e. g. Carlsbad, Marienbad, Tarasp*

and *Condal* waters, while in combination with magnesium sulphate it occurs in *Aesculop, Hunyadi Janos, Pullna, Apenta* and *Kissingen* waters. *Friedrichshall* water contains sodium chloride in addition to the above mentioned ingredients. These mineral waters may be taken with advantage in chronic constipation. When a complete evacuation is required they are generally combined with some vegetable purgative, as pulvis jalap. co., and mistura sennae co. When we want to drain out fluid from the body as in dropsy, pleurisy, ascites, etc., salines are either used in concentrated solutions (magnesium sulphate 5 dr. in 1 oz. of water), or given with some drastic purgative like jalap, where the effect of the latter drug reinforces the hydragogue action. As these salines are not cleansing, it is customary to precede their use by a vegetable or mercurial purgative. The usual practice is to give a dose of calomel or blue pill at night and to follow it up in the morning with a dose of black draught, Seidlitz powder, Glauber's salt, Epsom salt, or some natural mineral water.

In many cases the saline purgatives reduce the febrile temperature, and although they have no special action as intestinal antiseptics, they often reduce intestinal putrefaction by expelling the decomposing faecal matter.

The different mineral waters are often used daily to reduce body weight and to lower **blood pressure.** In the form of imperial drink the acid potassium tartrate is largely used by fever patients as a cooling and refreshing drink. Saline purgatives are extremely valuable in relieving portal congestion, and constipation associated with gout and uric acid diathesis.* Salines are largely used as an after-purgative with anthelmintics.

Sulphate of soda was considered almost a specific in **bacillary dysentery.** It has few advocates now and has been replaced by sulphaguanidine and sulphasuxidine. Moreover it is liable to aggravate dehydration. It is also used as a **diuretic** in cases of anuria in nephritis or due to the deposition of calculi in the renal pelvis during sulphonamide treatment. The suitable method is intravenous drip of 500 mils of a solution of sodium sulphate 4.3 p.c. with 10 p.c. glucose in normal saline 5 p.c. Epsom salt is an excellent purgative to counteract the constipating effect of iron in the treatment of anaemia.

Sodium phosphate being mild and almost tasteless is suitable for a delicate stomach and for administration to children. Acid sodium phosphate, being the natural acid of the urine, is largely used in 30 gr. doses to render the

* Sod. et pot. tart.	oz. 1½
Sod. sulph.	oz. 1½
Mag. carb.	grs. 240
Sod. bicarb.	oz. 1
Ol. menth. pip.	ms. 10

One teaspoonful or more in half a tumbler of water in the morning.

kaline urine acid. It is successfully used in the treat-ment of oxaluria and cystitis, particularly when due to *Bact. coli* infection.

2. Laxatives

AGAR. **Syn.**—Agar-agar.—Agar is a dried gelatinous sub-stance obtained from *Gelidium Amansii*, *G. cartilagineum*, *G. pris-toides* and other closely allied Rhodophyceae.

Characters.—In slender, translucent, nearly colourless, lustrous strips, 4 mm. ... bands about 4 cm. wide ; or a greyish white flakes or ... swells to a gelatinous mass when immersed in water. *Insoluble* in ... water, soluble when boiled with 100 parts of water, the solution forms a stiff ... on cooling.

Agar Pulvis. (Agar Pulv.). Powdered Agar.—Greyish-white.

B. P. Dose.—60 to 240 grs. or 4 to 16 grms.

Action and Uses.—Agar is largely used for preparing culture media for bacteriological purposes. It is taste-less, and when boiled with water or milk (1 in 200) forms into a jelly which may be given to invalids as food. Given internally mixed with milk, fruits or any other vehicle it is not absorbed and passes through the intestinal canal almost unchanged, only about 8 to 27 p.c. being utilised. During its passage through the gut it draws moisture and increases in bulk which stimulates peris-talsis and acts as a **mild laxative,** making the stool soft and bulky. It is valuable in habitual constipation, and may be combined with liquid paraffin or cascara.

3. Mild Purgatives

OLEUM RICINI. (Ol. Ricin.). **Syn. I. V.**—*Bheranda tel*, Beng. *Erand tel, Rendi tel*, Hind.

Source.—Castor oil is the fixed oil expressed from the seeds of ***Ricinus communis.***

Characters.—Viscid, nearly colourless, or pale yellow. Odour, slight ; taste, ... at first, acrid and unpleasant afterwards. *Solubility.*—1 in 3.5 of alcohol ...

Characters of the seeds.—Oval, compressed, shining marbled with reddish-... or black-brown spots or stripes. Kernel white, albuminous, enclosing a ... **dicotyledonous leaf.**

Composition. The chief constituent is (1) *Ricinolein*, a mixture of glycerides ... *Ricinoleic* acid, a viscid oil, believed to be the ... (2) *Glycerides of stearic and dihydroxystearic acid.*

B. P. Dose.—60 to 240 ms. or 4 to 16 mils.

Enters into.—Collod. Flex.

Pharmacology

Externally.—Castor oil is a bland fixed oil and has a soothing effect on the skin.

Internally. **Gastro-intestinal tract.**—Its local action on the stomach is the same as on the skin, unless it is rancid when it causes nausea, eructations and vomiting. It acts by the formation of alkali ricinoleate as a result of saponification in the duodenum, which gently stimulates the intestinal glands and peristalsis, and is a painless, ..., certain and fairly mild purgative operating within ... 6 hours. The stools are two to four in number, soft

or semiliquid, but not watery, the oil being expelled with the last ones and occasionally causing griping. A portion of the oil is no doubt absorbed and when excreted by the mammary gland it may cause purgation to suckling babies. Some patients get habituated to its use, and in others it sets up after-constipation like rhubarb. X-ray examination after castor oil has shown that the colon becomes flaccid and does not recover its normal tone and mobility for two to three days. This possibly explains the cause of after-constipation.

THERAPEUTICS

Externally.—It may be used like olive or almond oil. A drop of castor oil let fall on the conjunctiva allays irritation caused by a foreign body. It is employed as a basis of many hair-oils and pomades.

Internally.—It is the safest and best purgative for children, the old and infirm, delicate females, women during and after pregnancy, and persons subject to piles and fissure of the anus. In abdominal operations, pelvic diseases, peritonitis, fevers, especially in the constipation of typhoid fever, castor oil is the safest purgative to be used. Diarrhoea, infantile or otherwise, caused by indigestible or undigested food, yields to a dose of castor oil with or without a minute dose of tinct. opii. It is an excellent remedy for acute dysentery, when given with opium which prevents griping at the very onset. Similarly, in small doses (15 to 30 ms. with 5 to 10 ms. of tinct. opii emulsified) it is serviceable in the chronic variety. As an enema it has been given with success in impaction of the large intestine and rectum.

Prescribing hints.—It has been observed that a minimum dose of 30 ms. and a maximum dose of 8 ozs. are required to open the bowels of an adult. As a rule it is rarely necessary to use more than 4 to 6 drs. for a single dose to an adult. Children can bear sometimes large doses. A small teaspoonful is not a large dose for a new-born babe. The disagreeable smell and greasy and sickening taste can be overcome by using in the form of emulsion, or by giving in capsules. Taken floating on hot coffee, or half a teacup of warm water drunk two hours after a dose of the oil often helps its operation.

PHENOLPHTHALEINUM. (Phenolphthal.). Syn.—Purgen.—Phenolphthalein may be obtained by heating phenol with phthalic anhydride and sulphuric acid, and purifying the product.

Characters.—A white, or yellowish-white, crystalline or amorphous powder, soluble in alcohol (95 p. c.), almost insoluble in water. No odour, no taste.

B. P. Dose.—1 to 5 grs. or 60 to 300 mg.

Ol. ricin.	ms. 60-120.
Bism. carb.	grs. 7½
Tinct. opii	ms. 5-10
Mucil. trag.	q. s.
Syr. aurant.	ms. 60
Aqua menth. pip. ad.	oz. 1

Ol. ricin.	ms. 120-240
Mucil. acac.	q. s.
Syr. aurant.	ms. 60
Aqua Cinnam.	ad. oz. 1
A mild purgative.	

Official Preparation

Tabellae Phenolphthaleini. **B. P. Dose.—1 to 5 grs.** or **60 to 300 mg.** If the quantity to be contained in a tablet is not stated, 2 gr. tablets shall be supplied.

Action and Uses

Phenolphthalein is dissolved by the bile or alkali and produces a mild irritant action in both the small and large intestines producing soft motions in from 6 to 12 hours without any griping. For ordinary patients ½ to 3 grs. is a sufficient dose, but patients confined to bed may require as much as 10 grs. Part of the drug is absorbed and re-excreted in the bile and thus keeps up its action for several days. It has no action on the kidneys, but a small amount is excreted in the urine which it colours pink if alkaline. It is very safe and efficient in its action, but its use is contra-indicated in cases where there is a tendency to piles. It sometimes causes a rash in susceptible persons. Tetra-chlor-phenolphthalein given hypodermically (0.4 grm. in neutral olive oil 20 mils) is excreted by the bile and re-absorbed from the intestine and acts as a purgative.

The iodine compound of phenolphthalein (Iodophthalein) is moderately opaque to X-ray and is used to take photographs of the gall-bladder (*see* page 384).

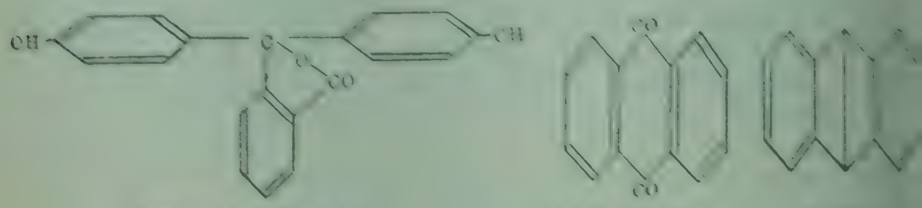
4. Anthracene Purgatives

The drugs of this group—aloe, rhubarb, senna and cascara—owe their properties to the presence of *anthracene* ($C_{14}H_{10}$) derivatives of anthraquinone. All contain *emodin* or trioxymethylanthraquinone; rhubarb and senna also contain *chrysophanic acid* or dioxymethylanthraquinone, which colours the urine yellowish-brown. They have an excellent action, being neither too mild nor too strong a purgative.

All these are valuable in habitual constipation, especially that of atonic type, but are not so good in spastic constipation, and in the presence of acid fermentation in the intestine there may be no cathartic effect. As a rule they do not act so well, or may fail in the absence of bile, but they may be made active by the addition of soap or an alkali. Their main action is on the large intestine, consequently they take about 10 to 14 hours to produce their effect. Straub and others have shown that the late effect of these drugs is due to absorption from the small intestine, where they are converted into active principles and reach the colon through circulation. It has been shown that senna is effective when given to anaesthetised cat intravenously or intramuscularly, and also when introduced into the jejunum even when the intestine has been divided to prevent direct passage of the drug into the large gut. Since they act by increasing the contraction of the

intestinal muscles they often cause griping and they ar largely combined with belladonna, hyoscyamus or som volatile oil.

The constitutional formula of Phenolphthalein, Anthraquino and Anthracene is given below :—



Phenolphthalein Anthraquinone Anthrace

ALOE. **Syn.**—*Musabar,* Beng. Hind.

Source.—Aloes is the residue obtained by evaporating to dryne the liquid, which drains from the leaves cut from various species *Aloe.* Known in commerce as Cape or Curacao (or Barbadoe aloes.

Characters.—Dark-brown or greenish-brown glassy masses ; transparent thin fragments (Cape aloes) ; or dark chocolate brown, opaque masses with a du waxy, uniform fracture (Curacao or Barbadoes aloes) ; odour characteristic ; tas nauseous, bitter. *Solubility.*—Almost entirely in alcohol (60 p. c.).

Composition.—(1) A crystalline glycoside, *Aloin* (Barbaloin). (2) *Aloe-emo* or trioxymethylanthraquinone. (3) *Resin.* (4) *Volatile oil, gallic acid,* a trace.

Aloes Pulvis. (Aloe. Pulv.).—Powdered Aloes is yellowis brown to dark reddish-brown.

B. P. Dose.—2 to 5 grs. or 0.12 to 0.3 grm.
Enters into.—Ext. Colocynth. Co., Pil. Colocynth. et Hyoscy., Pil. Rhei Co.

OFFICIAL PREPARATION

1. **Pilula Aloes.—B. P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.**

NON-OFFICIAL PREPARATIONS

1. **Pilula Aloes et Ferri, I. P. L.—About 4/5 gr. iron sulphate or 1/4 gr.** iron in each 8 gr. pill. **Dose.—4 to 8 grs. or 0.25 to 0.5 grm.**
2. **Pilula Aloes et Asafoetidae, I. P. L.—Dose.—4 to 8 grs. or 0.25 to 0.5 gr**

ALOINUM. (Aloin.).—Aloin is a mixture of crystalline pri ciples obtained from aloes.

Characters.—A pale yellow, microcrystalline powder ; inodorous ; taste, bitt *Solubility.*—Almost entirely in water, in alcohol (90 p. c.).

Composition.—*Barbaloin* and *isobarbaloin* in equal proportions. *Barbaloin* a *methyl-anthraquinone* derivative of a glycosidal character.

B. P. Dose.—1/4 to 1 gr. or 15 to 60 mg.

PHARMACOLOGY

Internally. **Gastro-intestinal canal.**—As a purgati aloes owes its property to the presence of glycosides the anthraquinone derivative which are slowly hydrolys in the intestine by the bile which irritate the colon a stimulate the peristalsis. Its action is slow taking 10 12 hours to purge. Large doses do not necessarily a earlier, but operate more violently and are accompani by pain, griping, tenesmus and even bleeding from t rectum. In moderate doses the stools are soft, dar coloured and formed and in large doses they are liqu

Soap or alkalies combined with it help its solution, and to a certain extent prevent griping. It increases the vascularity of the rectum, therefore the constant use of aloes may cause haemorrhoids. Aloin causes less griping.

Uterus.—Aloin injected into animals stimulates uterine muscle, and its administration by the mouth is followed by increased contraction. Moreover by stimulating the pelvic circulation it causes congestion of the uterus. It is therefore an emmenagogue and may act as an abortifacient when given to pregnant women.

Elimination.—Emodin is excreted in large quantities with the milk, and suckling babies are purged when it is given to their mothers. Aloes is also eliminated to a slight extent with the urine.

Therapeutics

Internally.—Aloes is a valuable purgative in chronic and habitual constipation and is ordinarily given in the form of a pill with rhubarb, nux-vomica, ipecacuanha or colocynth.* Its griping property is corrected by carminatives and extract of belladonna or hyoscyamus.

Female diseases.—Because it causes pelvic congestion, aloes is used in amenorrhoea and delayed menstruation, especially when associated with chronic constipation. When given with iron as Pilula Aloes et Ferri, it is very useful in anaemia, chlorosis and amenorrhoea of young girls.†

Caution.—Aloes is contra-indicated in pregnancy; irritable condition of the pelvic organs, especially rectum, haemorrhoids, menorrhagia, and during the nursing period of mothers.

RHEUM. Syn.—Rhei Rhizoma; Turkey Rhubarb.

Source.—Rhubarb is the rhizome of *Rheum palmatum*, and other species and hybrids of *Rheum*, excepting *Rheum rhaptonticum*. **Cultivated in China and Tibet.**

Characters.—In compact subcylindrical, barrel-shaped, conical or plano-convex, or [illegible] pieces. The surface sometimes covered with a bright yellowish-brown powder. Rounded or angular, smooth, showing beneath dark red lines, intermixed with the [illegible]-brown substance of the root, usually presenting small scattered [illegible]. Odour, characteristic, aromatic. Taste, bitter slightly astringent.

Composition.—(1) *Chrysophanic acid* or dioxymethylanthraquinone. (2) *Emodin*, or [illegible]anthraquinone. (3) *Rhein*, and (4) *Rheo-tannic acid*. (5) Oxalate of lime, rheumic acid, resin, starch, etc.

Rhei Pulvis. (Rhei Pulv.).—Powdered Rhubarb is orange yellow to yellowish-brown powder.

B. P. Dose.—3 to 15 grs. or 0.2 to 1 grm.

Official Preparations

1. **Pilula Rhei Composita.—B. P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.**
2. **Pulvis Rhei Compositus.** *Syn.—Gregory's Powder.*—Rhubarb 15 grs. in 60 grs.—B. P. Dose.—10 to 60 grs. or 0.6 to 4 grms.
3. **Tinctura Rhei Composita.**—10 p. c. **B. P. Dose.—30 to 60 ms. or 2 to 4 mils.**

*Aloin.	gr. 4
[illegible]	gr. 1/4
Pulv. Ipecac.	gr. 6
Ext. bellad. sicc.	gr. 1½
[illegible]	q.s.
Mass into 20 pills	

† Pil. aloes et ferri
Pil. aloes et myrrh. aa gr. 2
Ext. hyoscy. sicc. gr. 1/4

Non-official Preparation

1. Red Mixture. (Goodeve's).—Mag. carb. pond. 30 grs ; pulv. rhei [illegible] grs. ; sp. ammon. aromat. 30 ms. ; ol anise 2 drops ; aqua ad 1 oz. Dose [illegible] every 3 or 4 hours.

Pharmacology

Internally. **Alimentary canal.**—In small doses (2 5 grs.) rhubarb acts as a bitter **stomachic.** In large do (20 to 30 grs.), it increases the secretion of the inte nal glands and the peristaltic movements and acts a mild **purgative** within 4 to 8 hours and is often acc panied by griping, and the stool is liquid and yellow, colour being derived from the excess of bile and chrysa bin, the pigment. After opening the bowels the rh tannic acid produces constipation.

Elimination.—Chrysarobin has been found in the m and largely in the urine, both of which are coloured by Large doses may even lead to irritation of the kidney. makes the milk bitter and purgative.

Therapeutics

Internally.—Rhubarb is largely employed as a sto chic and laxative in infantile ailments. It is an excell remedy for the dyspepsia of children especially when cau by a faulty diet. It expels undigested food, and produ first a soothing and afterwards an astringent eff Gregory's powder and Goodeve's red mixture are use aperients for children.* With blue pill it makes excellent purgative for adults.†

SENNAE FOLIUM. (Senn. Fol.).—Senna Leaf consists dried leaflets of *Cassia acutifolia* (Alexandrian senna), and of *Ca* ***angustifolia*** **(Tinnevelly senna).**

Characters.—Pale greyish-green or yellowish-green, thin brittle ; 20 to 5[illegible] long and 5 to 16 mm. wide ; lanceolate or ovate-lanceolate ; unequal at the with entire acute lamina ; distinct veins on the under surface ; scattered ha[illegible] the both surfaces. Odour, slight ; taste, mucilaginous, slightly bitter, characteristic.

Composition.—Contains four glycosides (1) *rhein*, (2) *aloe-emodin*, (3) *ka* *ferol*, and (4) *isorhamnetin*.

Sennae Folia Pulvis. (Senn. Fol. Pulv.).—Powdered Senna I is green to yellowish-brown powder.

B. P. Dose.—10 to 30 grs. or 0.6 to 2 grms.

Official Preparation

1. **Pulvis Glycyrrhizae Compositus.**—Senna 16 p. c. **B. P. Dose.—60 to 12[illegible] or 4 to 8 grms.**

SENNAE FRUCTUS. (Senn. Fruct.). Senna Fruit. Sy Senna Pod.—The dried ripe fruits of *Cassia acutifolia* (Alexand senna pods) and of *Cassia angustifolia* (Tinnevelly senna pods)

Characters.—Alexandrian fruit, pale green with a brown central area and thin, broadly oblong or somewhat reniform ; 4 to 6 cm. long and up cm. wide ; rounded at the apex, base sometimes ending in a short stalk. Pe[illegible]

* Hydrarg. c. cret.	gr. 1/6	†Pil. rhei co.
Pulv. rhei co.	gr. 2	Pil. hydrarg. aa gr. 2
Sod. bicarb.	gr. 2	Ext. hyoscy. sicc. gr. 1/4
		At bed time to be followed in th morning by a saline.

and membranous, with about 6 flattened, obovate-cuneate seeds. Odour and taste, slight.

B. P. Dose.—10 to 30 grs. or 0.6 to 2 grms.

Official Preparations

1. Extractum Sennae Liquidum.—B. P. Dose.—10 to 30 ms. or 0.6 to 2 mils.
2. Syrupus Sennae.—[illegible] B. P. Dose.—30 to 120 ms. or 2 to 8 mils.
3. Infusum Sennae Concentratum.—B. P. Dose.—30 to 120 ms. or 2 to 8 mils.
4. Infusum Sennae.—B. P. Dose.—1/2 to 2 ozs. or 15 to 60 mils.
5. Mistura Sennae Composita. *Syn.—Black Draught.*—B. P. Dose.—1 to 2 ozs. or 30 to 60 mils.

Pharmacology

Senna is a **laxative** or brisk **purgative** according to the dose used. The anthraquinone derivatives stimulate both the secretion and peristaltic action of the intestines, almost entirely the large intestine, and produce pale yellow watery stools containing some undigested food. Large doses cause griping. It may cause the urine, if alkaline, to be red. It is eliminated with all the secretions and will purge the child when given to nursing women.

Therapeutics

Senna is a safe purgative in cases of simple constipation and faecal accumulation, but, on account of its tendency to gripe and nauseous taste, it should be combined with carminatives.

It is largely used *to complete the effect of duodenal purgatives* in the form of a blue pill at bedtime and black draught in the morning. The compound liquorice powder is to be preferred to the black draught, as it is a very nasty mixture. The compound liquorice powder is largely used in habitual constipation and the constipation of pregnancy. Since senna causes pelvic congestion it should be avoided in haemorrhoids and menorrhagia.

Prescribing hints.—The griping property of the black draught may be prevented by adding a few minims of tincture hyoscyamus. In the form of compound liquorice powder senna is largely used as a safe mild purgative. The simplest way of taking senna is to soak six to eight or more pods in cold water for 12 hours and to drink the infusion. It is more active and causes less griping, and is very useful in cases of habitual constipation.

CASCARA SAGRADA. (Casc. Sagr.). **Syn.—Rhamni Purshiani Cortex; Sacred Bark.—Cascara Sagrada** is the dried bark of *Rhamnus Purshianus* (California buckthorn). Collected at least one year before being used.

Characters.—In quilled, channelled, or nearly flat pieces, 1 to 4 mm. thick, 5 to 20 cm. in length. Cork smooth, purplish-brown, almost covered with patches of silvery-grey lichens. Inner surface reddish-brown, longitudinally striated. Odour characteristic. Taste nauseous, bitter and persistent.

Composition.—(1) *Emodin*, and (2) an allied substance possibly identical with *Frangula-emodin*. Also contains fat (2 p.c.), glucose, etc., volatile oil.

Cascarae Sagradae Pulvis. (Casc. Sagr. Pulv.).—Powdered Cascara Sagrada is light yellowish-brown to olive-brown powder.

Official Preparations

1. Extractum Cascarae Sagradae Siccum.—B. P. Dose.—2 to 8 grs. or 0.12 to 0.5 grm.
2. Extractum Cascarae Sagradae Liquidum.—B. P. Dose.—30 to 60 ms. or 2 to 4 mils.

3. **Elixir Cascarae Sagradae.—B. P. Dose.—30 to 60 ms. or 2 to 4 mils.**

PHARMACOLOGY AND THERAPEUTICS

Cascara is a laxative, producing healthy, copious and bilious stools in 8 to 12 hours. In large doses it is a gastro-intestinal irritant.

Cascara is a valuable aperient for habitual constipation. The dose ought to be so regulated as to produce a soft, painless, natural motion every morning, and when the desired end is gained, it should then be gradually reduced. The great advantage of the drug is that the dose does not require to be increased to maintain its action. However, for the successful cure of constipation it must be continued for at least 2 or 3 months.

Prescribing hints.—The dry extract is best given in pills either alone or with nux vomica and aloes. The nauseous taste of the liquid extract may be concealed by aromatics and glycerin or aromatics and chloroform. The plain aromatic syrup is not an unpleasant vehicle. The elixir is a pleasant preparation. The uncertainty of its action is sometimes annoying. This chiefly arises from the use by the manufacturers of inferior bark or the bark of allied species.

5. DRASTIC PURGATIVES

IPOMOEA. (Ipom.). Ipomoea. **Syn.**—Mexican Scammony Root. Scammony Root. Orizaba Jalap Root.—Dried root of *Ipomoea orizabensis.*

Characters.—In irregular, tough or fibrous pieces, of varying size and shape: often in portions, 3 to 10 cm. wide and 0.5 to 4 cm. thick, which are transverse slices of large roots. Externally dark greyish-brown and wrinkled, internally greyish or brownish. Slight odour; taste, faintly acrid.

Ipomoeae Pulvis. (Ipom. Pulv.).—Powdered Ipomoea is light grey to greyish-brown powder.

IPOMOEAE RESINA. (Ipom. Res.). **Syn.**—Scammony Resin. —Ipomoea Resin is a mixture of resins obtained from Ipomoea.

Characters.—Brownish, translucent pieces, brittle. Fracture resinous. Odour, characteristic, fragrant. Does not form an emulsion with water. Soluble in alcohol (90 p.c.) and in solvent ether.

B. P. Dose.—1/2 to 3 grs. or 30 to 200 mg.
Enters into.—Ext. Colocynth. Co., Pil. Colocynth. et Hyoscy.

PHARMACOLOGY AND THERAPEUTICS

Ipomoea or ipomoea resin is a drastic purgative. It becomes active only when it mixes with the bile in the duodenum. It is the taurocholate and glycocholate of soda of the bile that help its activity. It powerfully stimulates (*a*) the secretion of the intestinal glands, and (*b*) the muscular coat, though the contraction is irregular. As a result, free purgation occurs with griping in about two to four hours; the stool is first soft, soon becomes thin and watery. Ipomoea therefore is a smart hydragogue purgative. In large doses it causes gastro-enteritis.

They are largely used as ext. colocynth. co. or pil. colocynth. et hyoscy.

On account of its hydragogue properties it can be given in cases where depletion is necessary, as in apoplexy or cerebral congestion or where some effused fluid is to be absorbed, as in dropsy.

It can be used for the expulsion of intestinal worms after a dose of santonin and to complete the effect of anthelmintics for round and tape-worms.

JALAPA. (Jalap.). B. P. C.—Jalap consists of the dried tubercles of *Ipomoea purga.*

Characters.—Dark brown ; oblong, napiform or fusiform ; 3 to 15 cm. long ; larger ones incised ; hard, compact, and heavy. Externally furrowed, wrinkled with small transverse scars. Internally yellowish grey to dingy brown. Transverse section shows irregular, dark concentric lines. Odour, characteristic. Taste, sweet at first, acrid and disagreeable afterwards.

Composition.—(1) *Resin* 9 to 18 p. c., it appears to be identical with the resin obtained from ipomoea root. (2) *Jalapin* 10 p. c. insoluble in solvent ether, also termed *Convolvulin* and *Jalapurgin.*

Non-official Preparation

1. **Pulvis Jalapae Compositus,** B.P.C. Jalap 30 p.c., acid pot. tartrate and ginger. **Dose.**—10 to 60 grs. or 0.6 to 4 grms.

Pharmacology and Therapeutics

Jalap closely resembles ipomoea in action with this difference, that (1) it is less irritant and causes less griping ; and (2) it produces a greater stimulation of the intestinal glands and is therefore more hydragogue. It does not purge unless the resin is hydrolysed by the alkaline juice and bile in the intestine. *Small doses* have a laxative effect, but large ones produce several watery stools with pain and griping.

Being a hydragogue purgative, Pulv. Jalap. Co. is used in drawing off water in dropsy, ascites and anasarca from whatever cause they may arise. It is also used in obstinate constipation, in congestion of the brain and apoplexy. Jalap is an excellent purgative in Bright's disease and uraemia. It should not be prescribed where the bowels are inflamed or liable to inflammation.

OLEUM CROTONIS, B. P. C. **Syn.**—Oleum Tiglii.—Croton oil expressed from the seeds of *Croton Tiglium.* Brownish-yellow to dark reddish-brown viscid oil ; odour, disagreeable. Taste, acrid, burning. Contains (1) *Croton resin* a powerfully vesicant substance, appears to be the active principle. (2) Glycerides of stearic, palmitic, lauric, oleic, linolic and tiglic acids.

Identification of seeds.—The seeds are oval or oblong, dark brown, marked with ramification of the raphe. They resemble castor-oil seeds, which are brighter, polished and mottled.

Dose.—1/2 to 1 min. or 0.03 to 0.06 mil.

Action and Uses.—It is a powerful irritant to the skin. When taken internally undiluted it irritates the mouth and fauces, followed by griping. It is a drastic purgative. It is used only when the patient is unconscious as in *cerebral haemorrhage, coma* and in insanity on account of the minute dose and rapid and complete evacuation of bowels which follows. It is best given in pills, or mixed with butter or honey and placed at the back of the tongue.

COLOCYNTHIS. (Colocynth.). Colocynth. **Syn.**—Colocynthidis Pulpa ; Bitter Apple ; *Makhal phal,* Beng. *Indrabaruni,* Sans.

Source.—The dried pulp of the fruit of *Citrullus Colocynthis.*

Characters.—Odourless ; taste, intensely bitter. White or pale yellowish-white, light pithy fragments, and smaller broken fragments ; externally convex with ridges and flattened areas, internally irregularly concave and showing numerous seeds. Seeds flattened, ovoid, yellowish-white to dark brown.

Composition.—(1) *Colocynthin,* a bitter amorphous purgative resin. (2) An amorphous purgative alkaloid, *colocynthine. Mucilage, gummy matter.*

Colocynthidis Pulvis. (Colocynth. Pulv.).—Powdered Colocynth is yellowish white powder.

Official Preparations

1. **Extractum Colocynthidis Compositum.—B. P. Dose.—2 to 8 grs. or 0.12 to 0.5 grm.**

2. **Pilula Colocynthidis et Hyoscyami.—12.5 p. c. B. P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.**

Pharmacology and Therapeutics

Internally.—It is an irritant to the stomach and may cause nausea and vomiting. In moderate doses it stimulates the intestinal glands and the peristalsis causing watery evacuations and griping. Hence it is a hydragogue purgative. In large doses these actions are aggravated with intense gastro-intestinal irritation, reflexly affecting other abdominal and pelvic organs. It may therefore cause abortion if given to pregnant women.

Colocynth is often given in combination with aloes and mercury in constipation due to hepatic disorder. It is an excellent purgative to relieve portal engorgement. It should always be given with hyoscyamus or belladonna to prevent griping. Hence pil. colocynth. et hyoscyami is a valuable preparation. Because of the watery character of the stools, it may sometimes be given in **ascites, dropsy** or **cerebral congestion.**

Caution.—It should not be given either to pregnant women or to persons who are subject to diarrhoea, dysentery, piles or gastro-intestinal congestion.

6. Cholagogue Purgatives

PODOPHYLLUM. (Podoph.). Podophyllum. **Syn.**—Podophyllum Root; Podophylli Rhizoma.—The dried rhizome and roots of *Podophyllum peltatum*, American mandrake.

Characters.—Nearly sub-cylindrical, about 5 mm. thick; externally dark reddish brown, smooth, or slightly wrinkled cylindrical pieces, presenting at intervals enlargements, which are marked on the upper surface by a depressed circular scar, on the under surface stout, brittle rootlets, or their scars. Odour, characteristic. Taste, bitter, acrid.

Composition.—It is composed of (1) a neutral crystalline substance, *Podophyllotoxin* (0.2 to 1 p. c.), and (2) *Podophylloresin*, an amorphous resin, both of which are purgative. (3) *Picropodophyllin*, quercetin and starch.

Podophylli Pulvis. (Podoph. Pulv.).—Powdered Podophyllum is light brown.

B. P. Dose.—2 to 10 grs. or 0.12 to 0.6 grm.

PODOPHYLLUM INDICUM. Indian Podophyllum. **Syn.**—Podophylli Indici Rhizoma.—The dried rhizome and roots of *Podophyllum hexandrum*. Contains not less than 8.0 p.c. resin.

Characters.—Irregular and tortuous; knotty, 2 to 4 cm. long, and 1 to 2 cm. thick, flattened dorsiventrally, 3 to 4 cup-shaped scars on the upper surface; numerous root scars or stout roots on the under surface. Odour, slight, characteristic; taste, somewhat bitter and acrid.

Podophylli Indici Pulvis. (Podoph. Ind. Pulv.).—Powdered Indian Podophyllum is light brown.

B. P. Dose.—2 to 10 grs. or 0.12 to 0.6 grm.

Podophylli Resina. *Syn.—Podophyllin: Vegetable Calomel.* A mixture of resins, obtained from *Podophyllum*, or from *Indian Podophyllum*. Pale yellow to yellowish brown amorphous powder or brownish-grey masses; turns darker on exposure to light or heat. Characteristic odour, with bitter, acrid taste.

B. P. Dose.—1/4 to 1 gr. or 15 to 60 mg.

Pharmacology

Internally.—Being bitter and acrid in taste, podophyllin may excite salivation and nausea. In the intestine the resin is dissolved by the bile and in purgative doses causes griping and within 10 to 12 hours, a free watery stool, thus acting as a powerful hydragogue. Much of the force of the drug is directed to the small intestine, more especially the duodenum, whose contents it sweeps along rapidly, in which respect it resembles calomel. Impure resin produces more griping and common salt increases its cathartic effect. In large doses it gives rise to gastro-intestinal irritation. As a purgative its action varies with different individuals.

Liver.—The bile found in the faeces is due to diminished absorption owing to more rapid peristalsis not giving time for such absorption.

Therapeutics

Externally.—Application of podophyllin (5, 10 or 25 p.c. suspension in liquid paraffin), or an ointment (20 p.c.) is used in condyloma, lympho-granuloma inguinale and cutaneous carcinoma. The ointment may cause inflammation of the healthy surrounding tissue and should be avoided by applying some anaesthetic ointment.

Internally.—As a purgative it is an excellent remedy for constipation, due to hepatic disorder or otherwise ; the griping being corrected by hyoscyamus, belladonna, or cannabis indica. Its action becomes more uniform and certain when combined with other purgatives, *e.g.* aloes, jalap, colocynth, rhubarb.* It is best suited for constipation caused by the torpid condition of the liver, biliousness or hepatic dyspepsia. $\frac{1}{8}$ to $\frac{1}{4}$ gr. may be recommended as an ordinary dose for habitual constipation, but $\frac{1}{4}$ to $\frac{1}{2}$ gr. should be given in obstinate constipation or to relieve portal congestion.

EUONYMUS, B.P.C.—Euonymus consists of the dried root-bark of *Euonymus atropurpureus.*

Composition.—(1) A bitter crystalline alcohol *euonymol*, (2) the sterols, euonysterol, atropurpurol, and a mixture of fatty acids.

Non-official Preparations

1. **Extractum Euonymi, B.P.C.** Syn. *Euonymin. Dose.* 1 to 2 grs. or 60 to 120 mg.
2. **Tinctura Euonymi, B.P.C.** Bark 4, alcohol (45 p.c.) q.s. to 20. *Dose.*—15 to 40 ms. or 0.9 to 2.6 mils.

Action and Uses.—The action of euonymin resembles in many respects that of podophyllin, but is milder. It is a very useful

* Podoph. res.	gr. 1/6
Pulv. ipecac.	gr. 1/6
Ext. euonym.	gr. 1
Ext. nuc. vom. sicc.	gr. 1/6
Ext. hyoscy. sicc.	gr. 1/4
Pil. rhei co.	gr. 2

Pill for habitual constipation with torpid liver

remedy in hepatic disorders, and in constipation, especially when is due to torpidity of the liver. Combined with cascara, it may given with very good results in chronic or habitual constipa The following powder is very useful in infantile hepatic enlarg ment with slow fever.*

GROUP XI

DRUGS ACTING ON THE LIVER

The liver is by far the largest gland in the body an plays an important part in the general metabolism. An derangement of its functions upsets the whole metabol balance and produces diverse symptoms. It performs th following important functions :—(1) *Formation of bil* which is partly secretory and partly excretory. It form the bile pigment from the disused haemoglobin which i excretory, and any disturbance of this function is charac terised by jaundice, due to failure of the organ to excret bilirubin. These pigments take no part in the digestiv process but get mixed with the food in its passage throug the intestine where they are broken up by the bacteria activity. The bile acids are secretory and help in the ab sorption of fats. These acids, or their products of de composition, are partly absorbed from the intestine an are re-excreted by the liver. In the liver they stimulat the secretory cells and act as *natural cholagogues.* (2 *Plays an important part in iron metabolism*, by conservin organic iron and forming haemoglobin. It stores the anti anaemic factor, formed by the interaction between the in trinsic factor in the gastric juice and the extrinsic facto in protein food, which is essential for the development o megaloblasts into normoblasts and reticulocytes in th bone-marrow. It is also supposed to help normal coagu lation of the blood by forming fibrinogen. (3) *Regulatio of carbohydrate metabolism.* By removing the excess o sugar from the portal blood and storing the excess a glycogen it maintains the concentration of sugar in th blood at a constant level of 0.12 p.c. In this function i is helped by the hormones of the pancreas, the adrena medulla, the thyroid, and the pituitary gland. (4) *Regula tion of protein metabolism.* It helps to metabolise amin acids which are absorbed from the intestine the end pro ducts of protein digestion. The ammonia salts formed a the result of protein digestion are converted into harmles urea. (5) *Detoxicating functions.* It protects the bod from the action of toxins either produced during meta

* Ext. euonym.	gr. 1/2
Pulv. ipecac.	gr. 1/6
Salicin.	gr. 1
Pulv. rhei co	gr. 2
Sod. bicarb	gr. 2

taken or absorbed from the intestine. Many drugs are excreted in the bile which clears the system of these substances. But the important property of the liver is to detoxicate many drugs either by splitting them up to form harmless compounds, or by forming inert compounds, or by storing them in the organ to be excreted slowly. Thus ammonia is converted into urea, most of the barbiturates are broken down to inert compounds, chloral combines with glycuronic acid to form urochloralic acid, sulphonamides become acetylated, which though not less toxic is rapidly excreted. Since heavy metals cannot be broken down or synthesised to form some harmless compounds these are removed from the blood, stored in the liver and excreted slowly. (6) *Regulation of fat metabolism.* The absorption of fat from the intestine is helped by the presence of bile. This fat is transformed into lecithin in the liver and sent to the tissues. In certain conditions the fat content of the liver is increased, *e.g.* during starvation, in diabetes, in phosphorus and arsenic poisoning and is antagonised by choline. (7) *Regulation of uric acid metabolism.* This is not of much value in man.

Drugs that influence the secretion of bile.—Bile is being continually secreted by the liver, and the gall-bladder acts as a storage reservoir and ejects it intermittently into the intestine during digestion. The contraction of the gall-bladder is due partly to nerves and partly to hormones. Stimulation of the vagus causes contraction of the gall-bladder and relaxation of the sphincter oddi at the lower end of the bile duct. Stimulation of the sympathetic has the opposite effects. Normally the entrance of the chyme into the duodenum is followed by contraction of the gall-bladder and this has been attributed to a hormone *cholecystokinin* formed in the duodenum by the entrance of acid chyme from the stomach. The formation of secretin has also a stimulating effect both on the contraction of the gall-bladder and on the formation of bile. Secretion of bile salts is low during fasting and with carbohydrate rich diet, while protein rich diet increases it. It is evident therefore that there are several ways in which drugs may act as cholagogues. Thus magnesium sulphate in the intestine causes contraction of the gall-bladder, and the presence of acid in the duodenum helps formation of secretin. It does not mean that simply because more bile appears in the stool there is an increased secretion of bile; either the gall-bladder or the ducts have emptied more thoroughly, or the bile poured into the duodenum has been swept down without giving time for reabsorption. Cholagogues are now considered under two groups, namely:

Drugs which increase the secretion of bile are known as choleretics (on the analogy of diuretics).—

By far the best cholagogues are bile and bile acids. They are taurocholic and glycocholic acids, preparations of bile, desoxycholic and dehydrocholic acids and their salts. All, except dehydrocholic acid, increase the absorption of sterols in the intestine. They increase both the quantity secreted and also the bile salt concentration: then come the salicylates, which increase the volume of bile produced but diminish its total solids, soap and dilute hydrochloric acid. Potassium salts are choleretics. A high protein diet increases the secretion of bile, carbohydrates do not. Alcohol and narcotics diminish the secretion.

The use of choleretics is indicated when there is reason to believe that the secretion of the bile needs stimulation. Bile salts are indicated when it is desired to make the bile a better solvent for cholesterol or better digestive juice for the absorption of fats, sterols and fat soluble vitamins.

Drugs which empty the gall-bladder and cause an increase of bile-flow without necessarily increasing the amount secreted are known as **cholagogues.**—They act by stimulating contraction of the gall-bladder. Fats, yolk of egg, olive oil and castor oil accelerate emptying of the gall-bladder. Similarly, magnesium sulphate hypertonic solution (33 p.c.) helps expulsion of bile. The following drugs have a reputation of being cholagogues (formerly known as indirect cholagogues), *viz.*, podophyllum, euonymus, ipecacuanha, mercurials, and histamine. Wittkower found that while fear and joy increased bile flow, anger stopped it completly, as is wellknown, a meal taken in anger is badly digested.

Drugs used to dissolve gall-stones are called biliary lithontriptics.—Inflammation of the gall-bladder or cholecystitis is a common affection and is often due to some bacterial infection. The chief organisms responsible are *Bact. coli*, *streptococcus*, and *Bact. typhosus* or *Bact. paratyphosus*. It may also result as an extension of inflammation from the duodenum. This is often associated with gall-stones. Gall-stone formation is helped by decrease of bile salts which keep the cholesterol in solution. For this reason the bile salt content is an important factor. The so-called biliary stasis and the failure of the gall-bladder to empty properly is rarely due to weakness on the part of the gall-bladder to contract properly, but is commonly the result of reflex spasm which prevents the outflow of bile. This requires to be treated with sedatives, and the best sedative is belladonna. Several drugs have been used in cholecystitis, the most commonly used drug is hexamine. In some cases specific vaccine gives good result. The treatment of gall-stones by drugs is very unsatisfactory. The following are used to expel, reduce or dissolve the stones, *viz.*, sodium salicylate and aspirin, olive oil, etc.

Drugs which influence the glycogenolytic function.—*Glycolysis* is increased by adrenaline, ephedrine, thyroxine, ether and chloroform. These cause glycosuria by mobilizing hepatic glycogen. Glycolysis is diminished by insulin, synthalin, and to some extent by opium, codeine and bile salts. These prevent glycosuria.

Drugs acting on the liver cells.—Certain foods exert a great influence on the liver cells. Thus glucose protects the liver from the effects of carbon tetrachloride, while a rich carbohydrate diet protects the liver from chloroform poisoning, diet rich in fat predisposes to intoxication. Administration of glucose is better than giving food rich in starch since it requires to be digested before it can be utilised as sugar. Next to glucose is calcium, and then comes alkalies, chiefly bicarbonate of soda. Choline, cystine and methionine also protect the liver from these poisons.

Drugs having a toxic effect on the liver.—From what has been said before it is evident that the liver acts as a gate keeper and detoxicates, synthesises, stores, breaks down and excretes most of

the poisonous drugs. But the organ frequently suffers from the effects of many of the poisonous drugs, even though it has a remarkable power of recuperation, the damage is sometimes great. Toxic jaundice may follow administration of organic arsenicals. The drugs which produce toxic effects on the liver are the heavy metals, arsenic, antimony, phosphorus, cinchophen, carbon tetrachloride, and anaesthetics, chiefly chloroform, ethyl chloride, bromethol.

CHOLERETICS

EXTRACTUM FELLIS BOVINI. (Ext. Fell. Bov.). **Syn.—Fell Bovinum Purificatum.**

Source.—Extract of Ox Bile is obtained by evaporating fresh ox bile to one fourth of its volume, shaking it with alcohol (90 p.c.), filtering and evaporating the residue to the consistence of a firm extract. Contains the bile salts and pigments free from mucus.

Characters.—A dark yellowish-green, plastic substance; taste, bitter and disagreeable. *Soluble* in water, and in alcohol (90 p.c.).

B. P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

PHARMACOLOGY AND THERAPEUTICS

Internally.—Bile though bitter, it cannot replace vegetable bitters as a stomachic. Given by the mouth most of it is absorbed in the intestine and carried to the liver which excretes it again, a small quantity of the bile acids being eliminated with the urine. It is a valuable **choleretic** and increases the secretion of both the solids and the fluids of the bile. The bile acids irritate the mucous membrane of the colon and act in the absence of bile. Bile increases the lipolytic ferment of the pancreas and helps the absorption of fats, and is therefore used in those cases of dyspepsia and constipation in which the natural secretion of bile is very deficient. By helping intestinal digestion and absorption of fat, bile helps absorption of vitamin A, D and K. It is highly important in facilitating utilisation of vitamin K which is instrumental in maintaining the level of prothrombin in the blood. Twenty to 30 grs. of bile extract dissolved in 1 or 2 ozs. of water may be given as a clyster in cases of impaction of faeces in the rectum, where there is no room for a larger enema. It is generally given in cachets or in solution, but it is best administered in the form of keratin-coated or salol-varnished pills, two hours after food.

Dehydrocholic Acid. (Not official) Syn.—Decholin; Dehydrocholin. An oxidation product of cholic acid derived from natural bile acids.

Dose.—4 to 8 grs. or 0.25 to 0.5 grm.

ACTION AND USES.—It is a most powerful **choleretic** known and is used in all forms of hepatic derangements and helps drainage of the bile ducts by removal of inspissated bile, plugs of mucus, etc. It is therefore used in acute and chronic **cholecystitis, cholelithiasis** without complete obstruction, catarrhal and latent jaundice, cirrhosis of the liver and constipation due to biliary hyposecretion. In **cholecystography** it helps appearance of the gall-bladder shadow and helps removal of residual dye from the bile tract. It is useful in migraine when associated with or due to derangement of hepatic function.

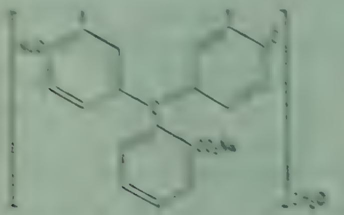
It is generally administered in capsules of 4 grs. (0.25 grm.) the sodium salt may be used parenterally in 5 to 10 mils of 20 p. solution.

Sodium dehydrocholate 10 mils of 20 p.c. solution is injec intravenously quickly to determine the arm to tongue rate of cir lation of the blood. The time taken from the injection to the appe ance of a bitter taste in the mouth is taken that of a complete c cuit. Normally it is 10 to 17 seconds; in failure of the heart, 20 40 seconds.

Drugs used for Diagnostic Purposes

1. For X-ray examination of the alimentary canal
   Barium Sulphate (see page 168), Bismuth Subnitrate (q.v.)
2. **For X-ray examination of the gall-bladder**
   Iodophthalein, Pheniodol
3. **For testing liver function**
   Laevulose (q.v.)

IODOPHTHALEINUM. (Iodophthal.). $C_{20}H_8O_4I_4Na_2$, $3H_2O$. Sy —**Iodo-ray; Opacin.**



$C_{20}H_8O_4I_4Na_2,3H_2O$ . . . . Mol. Wt. [illegible]

Source.—Iodophthalein is Di-sodi salt of tetraiodophenolphthalein. Prepa by the iodination of phenolphthalein. Con tains not less than 87 p.c. of phthale The separated phthalein contains 60 to p.c. of iodine.

Characters.—A blue or blue-viol crystalline powder. Odourless; tast saline, astringent. Soluble in 7 parts water. Slightly soluble in alcohol (90 p.c

B. P. Dose.—1/3 to 1/2 gr. per lb. body weight up to 75 grs. or 40 to 60 m per kg. of body weight up to 5 grm.

Uses

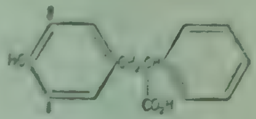
Given intravenously or *per os* it is excreted by the liver into t gall-bladder where it is concentrated rendering it opaque to X-ra Therefore it is largely used for diagnosis of **cholecystic diseases cholecystography.** For all practical purposes oral use is sufficie **intravenous use is necessary only** after negative results from o **use or when this route is not** practicable. The patient takes a lig evening meal at 7 p.m., and at 10 p.m. two keratin coated gela capsules of 5 grs. each are taken followed by a drink of wat Every fifteen minutes two capsules are taken at a time till t have been swallowed, accompanied by free drinks of water. fact the patient should keep drinking water till he falls asleep. food is given the following day. Examination is made to see t effect of meal upon the shadow.

Graham's technique for intravenous use is as follows:—T injection is given early in the morning, and no food is taken exc a glass of milk if hungry, although water may be drunk during t day. Three grammes (45 grs.) are dissolved in 40 mils (12 dr of triple distilled water and half the amount is injected slowly la ing 5 to 7 minutes; half an hour later the remaining half is injecte It is necessary to wash through the needle some normal salin

Nausea and vomiting with fall of blood pressure may oc occasionally and should be counteracted by injection of 10 m adrenaline solution. Forty grains of bicarbonate of soda in sol tion should be taken every three hours, day and night, as long the patient remains awake. Radiograms are taken 8 and 6 ho after the injection. The solution must be freshly prepared.

PHENIODOL. Syn. [illegible]—Pheniodol is [illegible] -3- [illegible] acid. A creamy white powd

[illegible] slight; taste, slight, later producing a tingling sensation in the mouth. Alkaline solutions have a bitter [illegible] taste. Almost *insoluble* in water; soluble in aqueous alkaline solutions and in alcohol [illegible].



B. P. Dose.—45 to 90 gr. or 3 to 6 grm. as a single dose.

Uses.—A contrast medium used for cholecystography. It is superior to iodophthalein being less irritant to the stomach, and is readily concentrated in the gall-bladder, giving a clear well-defined shadow without any systemic disturbance. It is administered in milk or other liquid at 6 p.m. and the examination is done the following morning, generally 16 hours after administration of the drug.

Technique and preparation of the patient is the same as for the oral use of iodophthalein.

GROUP XII

ASTRINGENTS

Astringents form a special group of drugs whose action is characterised by contraction or shrinkage of the tissues and diminished exudation or secretion. In the intestine their effects are antagonistic to purgatives. They include the *astringent metals, acid sulphuric dilute,* and *vegetable astringents.* Opium and chalk act as intestinal astringents by diminishing the secretions and peristalsis.

The *vegetable astringents* owe their property to the presence of tannin. They precipitate proteins and form a blue or black compound with iron preparations. They are milder in their effects than the astringent metals, and being practically harmless they are specially used in diseases of the alimentary canal. All astringents are *local haemostatics, i.e.* check bleeding by precipitating a hard coagulum which plugs the vessels (*see* page 304). They have no action on the vessel walls. Since astringents are precipitated by proteins they are not much absorbed, nor do they exist in the blood and tissues in sufficient quantity to be of any use. They have therefore no remote astringent effect and act only on the part on which they are applied.

Tannic acid or substances containing it form more or less insoluble compounds with many metals, alkaloids, glycosides, etc., and may be used as their antidotes.

Astringents are classified as follows:—

1. Metallic astringents: *see* page 117.
2. Vegetable astringents: Tannic Acid, Catechu, Rhatany, Hamamelis, Myrobalan (q.v.).

ACIDUM TANNICUM

(Acid. Tann.). Tannic Acid

Syn.—Tannin; Digallic Acid.

Source.—Obtained from the galls of various species of *Quercus*, by subjecting them to special fermentation.

Characters.—Yellowish-white or light brownish, glistening scales, light masses, or as amorphous powder; odour, characteristic; taste, strongly astringent.

Soluble in 1 part of water and alcohol (90 p.c.), freely in acetone, slowly in 1 of glycerin. An aqueous solution forms precipitates in solutions of gelatin, alb and some alkaloids.

Official Preparations

1. **Glycerinum Acidi Tannici.**—15 p.c.
2. **Suppositoria Acidi Tannici.**—3 grs. or 0.2 grm. in each.
3. **Trochisci Acidi Tannici.**—1/2 gr. or 30 mg. in each.

Non-official Preparations

1. **Pasta Acidi Tannici, B. P. C.** *Syn.*—*Tannic Acid Jelly.* Tannic acid tragacanth 30, chlorocresol 1, alcohol (90 p.c.) 80, water q.s. 1000.

2. **Acidum Acetyltannicum.** *Syn.*—*Di-Acetyl-tannin; Acetannin; Tann* —A product obtained by the acetylisation of tannic acid. A yellowish or grey white powder. Slightly soluble in water and in alcohol. In *enteritis* and *infan* *diarrhoea.* *Dose.*—5 to 10 grs. or 0.3 to 0.6 grm.

3. **Albumini Tannas.** *Syn.*—*Albutannin.*—A compound of albumin and ta acid. A yellowish-white, odourless powder. Almost insoluble in water. *Dos* 8 to 15 grs. or 0.5 to 1 grm.

4. **Tannoform.** *Syn.*—*Methyl Ditannin.*—Reddish-white powder insoluble water. As a dusting powder in *hyperidrosis, bed-sores, soft chancres, eczema,* Internally in *infantile diarrhoea.* *Dose.*—8 to 15 grs. or 0.5 to 1 grm.

Pharmacology

Externally.—Tannic acid has no action on the broken skin, but applied to an exposed mucous membra or a denuded surface it coagulates the mucous and t albuminous secretions, and forms a firm insoluble prote ive covering over the part. The coagulated albumin gelatin resists putrefaction. Absorbed into the tissu it coagulates the interstitial fluids, and condenses the alb minous and connective tissues, and thereby diminishes t serous discharge. Hence it is a powerful local **astringe** It arrests haemorrhage partly by plugging the sm vessels, and partly by the production of a coagulum in t surrounding tissues, but it has no action on the muscu coats. It is therefore a local **haemostatic.**

Internally. **Alimentary canal.**—Tannic acid cau dryness of the mouth with a feeling of astringency and stiffness of the tongue and throat, owing to the coagu tion of the secretions of the mucous membranes. Th effects are due to the direct chemical action on the prote In the stomach a portion of it is converted into tann when it loses its astringent property till the tannate albumin is redissolved in the gastric juice and tann again liberated. Pepsin and peptone are precipitated a neutral solution, therefore they are not affected beca of free acid, but large doses impair digestion by prec itating pepsin, and often cause gastric irritation and vom ing, but stop haemorrhage by local haemostatic proper In the intestine it causes constipation by precipitating p teins and diminishing the glandular secretions, thus ma ing the stools harder and drier. It precipitates yeasts a microbes and acts as a mild antiseptic and renders t faeces less offensive by decreasing the number of bacte The undecomposed tannates and unabsorbed gallates thrown off with the faeces. Tannic acid does not affect t biliary secretion.

Blood.—Tannic acid enters the blood mostly as gallates and partly as tannates and circulates as such.

Elimination.—There is a great diversity of opinion as to its excretion. According to some, any that has been absorbed is decomposed in the human body, only about 1 p.c. is detected in the urine or faeces ; although gallates and traces of tannates are found in the urine of animals. But Stockman found gallic acid with traces of tannin in the urine when pure tannin was given by the mouth ; and a large amount of tannin with a little gallic acid in the urine when sodium tannate was administered.

THERAPEUTICS

Externally.—As a *local haemostatic*, tannic acid is largely employed in haemorrhages from the nose, the rectum, the bladder, the urethra, etc. It may be used as a snuff or a nasal douche (5 p. c. solution) in epistaxis, or as an ointment or a suppository in haemorrhoids. As a *local astringent* it is useful in subduing mild forms of subacute or chronic inflammatory processes and discharges from the skin, as in eczema, intertrigo ; the ear, as in otorrhoea ; the eye, as in conjunctivitis and corneal vascularity (as collyrium 4 grs. to 1 oz.) ; the nose, as in ozaena (a douche, snuff or paint) ; the vagina, as in leucorrhoea (an injection, douche or pessary) ; the uterus, as in ulcerated os (pessary or cotton-wool soaked in tannic acid and glycerin) ; the bladder, as in cystitis (injection) ; and the rectum, as in ulcers, fissures and prolapse of the rectum (as **injection or suppository**).

It is used in the treatment of **burns**, and is applied as a dressing (5 p. c. solution for children and 10 p. c. for adults) which is kept saturated till the area is tanned mahogany brown. The jelly is a useful first-aid treatment for burns of minor degree. The value of this treatment depends upon the production of a tightly adherent rigid crust over the burnt surface. It diminishes pain, prevents fluid depletion, decreases toxaemia, and in the 2nd and 3rd degree of burns allows epithelisation to proceed while the membrane is in place. The great advantage of this treatment is the prevention of the absorption of toxin which generally causes death on the 2nd and 3rd day after the injury. When sprayed over the wound no dressing is applied and the spraying done every 15 minutes until a dry brown crust forms which seals the wound. There are however certain disadvantages of tannic acid, *viz.*, its solution is unstable, it has no antiseptic power, and it is not ectonic. It is therefore combined with gentian violet (1 p. c. aqueous solution) or acriflavine (1 in 1000) when used as a spray.

Internally. **Alimentary canal.**—Tannic acid makes a

very good dentifrice for bleeding and ulcerated gur Glycerin of tannic acid is a valuable application in ulc ative stomatitis, subacute or chronic sore-throat, relax or elongated uvula, enlarged tonsils, etc. A gargle (glyc acid. tann. 1 dr. to 1 oz.), a spray (1 dr. in rose wat 10 ozs.), or lozenges may be used in these cases. As sufflation, tannic acid with starch makes an excellent ap cation for the mouth and larynx. It is a valuable reme for gastric and intestinal haemorrhage, but it should given in large doses, say 30 to 40 grs. every one or t hours. It is a valuable **antidote** in poisoning by alkalo or metallic salts. It is largely used in diarrhoea, eith acute or chronic, but preparations of catechu are genera preferred.

Prescribing hints.—Internally it may be given in soluti cachets or pills. In the absence of tannic acid any vegetable in sion containing tannin, such as strong tea or decoction of oak ba may be employed in alkaloidal poisoning. It should not be co bined with ferric salts which it colours black ; with mineral acids precipitates tannin, and with alkalies it forms soluble tannates, b the solution changes colour becoming black. Caffeine is precipi ted by tannic acid but is redissolved if the latter be in excess.

CATECHU. (Catech.). Catechu. **Syn.**—Pale Catechu ; Gambi *Khayer*, Beng., *Kath*, Hind.

Source.—A dried aqueous extract of the leaves and young sho of *Uncaria Gambier.*

Characters.—In cubes, sometimes agglutinated. Each side about 25 mm. F greyish-brown to dark reddish-brown externally, pale brown internally ; por and friable. Taste, at first bitter and astringent, then sweetish. No od *Solubility.*—Entirely in boiling water.

Composition.—(1) *Catechu-tannic acid*, 22 to 50 p.c. (2) *Catechin*, 7 to 33 (3) *Quercetin*, catechu-red, *gambier-fluorescein*, wax, oil, etc.

Incompatibles.—Alkalies, metallic salts, gelatin.

Catechu Pulvis. (Catech. Pulv.).—Powdered Catechu is p brown.

OFFICIAL PREPARATION

1. **Tinctura Catechu.—1 in 5 B. P. Dose.—30 to 60 ms. or 2 to 4 mils.**

ACTION AND USES.—Catechu is a non-irritating astri gent, acting like tannic acid, which it contains. It is valuable *local astringent* and may be used in the form dentifrice, gargle, paint, or lozenge for spongy gum mercurial and ulcerative stomatitis and relaxed throa Catechu is a very useful remedy for diarrhoea.

KRAMERIA. (Kramer.). Krameria. **Syn.**—Rhatany Roo Krameriae Radix.

Source.—The dried root of *Krameria triandra*, known as Pe vian Rhatany.

Characters.—Nearly cylindrical, slightly flexuous, reddish-brown. 15 m thick ; cork, scaly with polygonal cells and dark-brown walls. Fracture, sho fibrous in the bark, splintery in the wood ; bark, bright reddish-brown abou third of the radius of the root in thickness. Wood, pale reddish-brown fi radiated in transverse section. Odourless. Taste of bark, astringent, wood nea tasteless.

* Tinct. Catech.	ms. 60
Glycer. Alum.	ad oz. 1

Composition.—(1) *Rhatania tannic acid*, 8.4 p.c. (2) Rhatania red, the colouring matter. (3) Rhatannin, neutral substance.

Incompatibles.—Alkalies, lime water, iron, lead salts and gelatin.

Krameriae Pulvis. (Kramer. Pulv.).—Powdered Krameria is reddish-brown.

B. P. Dose.—10 to 30 grs. or 0.6 to 2 grms.

Official Preparations

1. **Extractum Krameriae Siccum.—B. P. Dose.—5 to 15 grs. or 0.3 to 1 grm.**
2. **Trochisci Krameriae.** *Syn.—Krameria Lozenges.*—1 gr. or 60 mg. in each.
3. **Trochisci Krameriae et Cocainae.** *Syn.—Krameria and Cocaine Lozenges.*—1 gr. or 60 mg. of extract and 1/20 gr. or 3 mg. cocaine hydrochloride in each.

Action and Uses.—Rhatany is a powerful astringent, because of the tannic acid it contains. The powdered root forms an important ingredient in many dentifrices and an infusion of the root makes a good gargle in relaxed sore-throat, spongy and ulcerated gums and mercurial stomatitis. Krameria and cocaine lozenge is very efficacious in sore-throat.

HAMAMELIS. (Hamam.). Hamamelis. **Syn.**—**Hamamelidis Folia; Witch Hazel Leaves.**

Source.—The dried leaves of *Hamamelis virginiana*.

Characters.—Broadly oval, 7 to 15 cm. long, upper surface dark green or brownish-green, pale below, apex obtuse; base oblique, cordate and shortly petiolate; margin, sinuate; veins, pinnate and prominent on the under surface where it is furnished with stellate hairs. Taste, astringent, slightly bitter. No odour.

Composition.—(1) *Tannic acid.* (2) *Gallic acid*; a bitter principle; and a volatile oil.

Hamamelidis Pulvis. (Hamam. Pulv.).—Powdered Hamamelis is dull green.

Official Preparations

1. **Extractum Hamamelidis Liquidum.**
   (a) **Unguentum Hamamelidis.—Liquid extract 10 p.c.**
2. **Extractum Hamamelidis Siccum.**
   (a) **Suppositoria Hamamelidis.—3 grs. dry extract.**
   (b) **Suppositoria Hamamelidis et Zinci Oxidi.**—3 grs. dry extract and 10 grs. zinc oxide in each.

Action and Uses.—As a local astringent or haemostatic it has been used in various ways and in various affections in place of tannic acid. It may be used as a gargle in sore-throat, bleeding from the gums, ulcerative stomatitis, or as an injection in gonorrhoea, vesical haemorrhage, nasal catarrh, epistaxis, etc. The suppository may be used as a sedative and haemostatic in inflamed and bleeding piles.

GROUP XIII
ANTHELMINTICS

Infection of man and animals with different varieties of worms is a common occurrence and drugs which are used to kill or expel these worms are known as *anthelmintics*. Some of these live in the intestinal canal, while others in the tissues of the host and cause *somatic infections*. *Vermicides* are remedies which kill the worms, while *vermifuges* expel them without necessarily killing them. These terms are rarely used now. Active peris-

talsis tends to remove intestinal parasites with other in tinal contents. Thus drastic purgatives are sometimes u for the purpose of expelling the worms with partial ben Since the worms fix themselves with their hooks, suck or serrated margins, they must be weakened or narcoti or killed before they can be effectively expelled.

An ideal anthelmintic is one whose value depends only upon its poisonous effects on the parasites in intestinal canal, but also upon its harmlessness as rega the patient, *i.e.* the drug should exert its influence on worms without being absorbed, and since it is desired attack the worm rather than the host, the dose must as large as can be borne by the patient without produc any toxic effect. Safe doses of anthelmintics do not the parasites, but only depress or narcotise them. these would recover if left in the intestine. It is theref customary to follow their use with a purgative. T also prevents any absorption of the drug and so di nishes the toxicity. The choice of a preliminary p gative depends upon the nature of the anthelmi used. Thus for drugs like male fern, thymol, carbon te chloride, purgative oils should be avoided, since oil h absorption of these drugs. Whereas castor oil may used with oil of chenopodium. It has the advantage counteracting the paralysing action of oil of chenopodi on the intestine. Magnesium sulphate half an ounce water is an all round good purgative. Calomel may be used followed by magnesium. In large doses most thelmintics act as gastro-intestinal irritants.

In cases of infection with tape-worm or hook-wo the use of an anthelmintic is usually preceded by a fas that the parasite will not be protected by the intest contents. This however has the disadvantage of weak ing the patient and also helping absorption of the d In any case the fast should not be severe. In mass tr ment it is a great disadvantage and its use is disapp ing, specially with weak and debilitated patients. A a light evening meal a dose of purgative is given and anthelmintic is taken first thing in the following mor either in one dose, or in two or three divided doses gi every hour, to be followed two hours after the last dos another dose of the purgative. A preliminary saline gative often helps to remove intestinal mucus and t helps the exposure of the worms to the action of the ant mintic. Magnesium sulphate or sodium sulphate or may be used. Santonin is best given at bedtime on count of its effects on the retina.

A number of drugs belonging to other groups, for instance of turpentine, beta-naphthol and thymol also enjoy the reputati anthelmintics.

Anthelmintics are classified as follows :

Class A : Drugs acting on parasites which infest the intestines

I. **Those acting on Nematodes**

(a) Anthelmintics for round-worm : **Santonin, Oil of Chenopodium, Butea Seeds, Hexylresorcinol.**

(b) Anthelmintics for thread-worm : **Diphenan, Crystal Violet, Carbon Tetrachloride, Tetrachloroethylene, Hexylresorcinol, Phenothiazine.** Rectal injections of a solution of **common salt,** strong infusion of **Quassia** and **Calumba** and solution of **Ferric Chloride.**

(c) Anthelmintics for hook-worm : **Thymol** (q. v.), **Betanaphthol** (q. v.), **Carbon Tetrachloride, Oil of Chenopodium, Tetrachloroethylene, Hexylresorcinol.**

(d) Anthelmintics for whipworm (*Trichuris*) : **Hexylresorcinol, Tetrachloroethylene, Oil of Chenopodium.**

(e) Anthelmintics for strongiloides : **Crystal Violet.**

II. **Those acting on Cestodes**

Anthelmintics for tape-worm : **Male Fern, Pelletierine Tannate, Carbon Tetrachloride, Tetrachloroethylene, Melon Pumpkin Seeds** (q. v.).

Class B : Drugs acting on parasites which infest the tissues of the host

I. **Those acting on Trematodes or Flukes**

(a) For Bilharziasis : of the three species, viz., B. haematobium, B. mansoni and B. japonicum, B. haematobium is amenable to treatment : **Sodium Antimonyltartrate, Stibophen** (Fouadin). **Emetine.**

(b) For Fasciolopsis buskii : **Thymol, Betanaphthol, Carbon Tetrachloride,**

(c) For Fasciola hepatica (liver fluke) : **Emetine.**

(d) For Chlonorchis sinensis: These inhabit the gall-bladder and biliary passages : **Crystal Violet.**

(e) For Paragonimus westermanii (lung fluke) : **Emetine** and **Tartar Emetic.**

II. **Those acting on Nematodes**

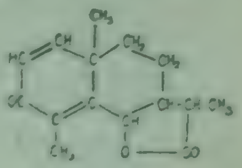
For Filariasis : **Sodium Antimonyltartrate, Stibophen (Fouadin), Arsenic, Hetrazan.**

1. Anthelmintics for round-worm

SANTONINUM

Santonin. (Santonin.). $C_{15}H_{18}O_3$

Source.—A crystalline lactone obtained from santonica, the dried unexpanded flower-heads of *Artemisia cina*, and other species of *Artemisia*.



Characters.—Colourless, flat, rhombic prisms, feebly bitter, turning yellow by sunlight. *Solubility.*—Almost insoluble in water, soluble in 2.5 parts of chloroform and in 50 parts of alcohol (90 p. c.).

B.P. Dose.—1 to 3 grs. or 60 to 200 mg.

PHARMACOLOGY

Internally.—Santonin is a direct poison to round-worms, *Ascaris lumbricoides*, killing them in the intestine. Its action is less marked on thread-worms, *Oxyuris vermicularis*, and it has no effect whatever on tape-worms. Some assert that it does not kill but paralyses the worm.

In fact many worms are passed out alive. It is partially dissolved in the stomach and passes into the intestine where it acts as an anthelmintic. This effect is possibly due to an unknown oxidation product formed in the intestine. Sometimes a portion may be absorbed and though this may not give rise to any toxic symptoms there is yellow vision (xanthopsia) and colouration of the urine.

Absorption.—It is oxidised in the tissues and is excreted in the urine and faeces in the form of oxysantonins. After a therapeutic dose the entire quantity is eliminated by the urine as a coloured substance although traces of santonin may be detected in the urine after large doses.

Nervous system.—It produces some curious effect here. Even in medicinal doses, within an hour or two after administration, objects first appear bluish, and then greenish or yellow, due perhaps to a certain disturbance of the retinal fibres, for though there is hyperaemia of the retina, yet the humours and other tissues of the eye are not stained. Taste and smell are sometimes affected.

Kidneys.—Santonin is chiefly excreted by the kidneys. Sometimes it may create dysuria or incontinence of urine in children. It colours acid urine greenish-yellow and alkaline urine purplish-red, referable probably to an unknown oxidation product formed in the system and excreted with the urine.

Toxic action.—In large doses it causes headache, vomiting, purging, loss of consciousness and speech, cold sweats, depression of the heart and respiration, intense saffron-coloured urine, tremor, convulsions and death. Sometimes a rash appears on the skin. Poisoning occurred in a child from 1½ grs. On the other hand, recovery has taken place after swallowing 1 oz. of the drug. These poisonous symptoms were probably due to impurities.

Therapeutics

Internally.—Santonin is chiefly employed for expelling round-worms. It should be given at night on an empty stomach, after a mild purge in the morning, followed by a purgative next morning. Calomel is the best purgative to use. To a child 1 to 3 years old 1 to 2 grs. of santonin may be safely given followed by a purgative next morning. The best method is to prescribe it with calomel and sugar, followed, if necessary, by a dose of Gregory's powder or a saline next morning. It should be taken for three alternate nights.

2. Anthelmintics for tape-worm

FILIX MAS. Syn.—Aspidium.—Male Fern consists of the rhizome, frond-bases and apical bud of *Dryopteris Filix-mas*, collected late in the autumn, divested of the roots and dead portions and carefully dried, retaining its internal green colour. Contains not less than 1.5 p.c. filicin.

Characters.—From 7 to 15 cm. or more long. Rhizome about 3 to 4 cm. in diameter, entirely covered with curved angular, dark-brown bases of the fronds, which bear numerous ramenta ; brown externally. Transverse section shows 7 to 9 pale yellow meristeles arranged in a diffuse circle. Odour, slight. Taste, first sweetish and astringent then bitter and nauseous.

Composition.—(1) *Filmarone*, $C_{47}H_{54}O_{16}$; an amorphous substance to which its properties are due, in solution it slowly decomposes into *Filicic acid* and *Aspidinol*. (2) *Albaspidin*. *Filicin* is an anhydride and a modification of filicic acid.

Filicis Pulvis. (Filic. Pulv.).—Powdered Male Fern.—Brown in colour.

Official Preparation

1. **Extractum Filicis.** *Syn.—Liquid Extract of Male Fern* ; *Oleoresina Aspidii.* —Contains 25 p.c. w/w of Filicin. **B. P. Dose.—45 to 90 ms.** or **3 to 6 mils.**

Pharmacology and Therapeutics

Internally.—Male fern is a safe and reliable anthelmintic for tape-worm (*Taenia solium, T. Mediocanellata* and *Dibothriocephalus*), but being a local irritant it causes vomiting. It should be given in fairly large doses (1 to 2 drs.) to adults on an empty stomach preferably in two divided doses, after the bowels have been cleared by a purgative, and should be followed again by a brisk purgative. It also expels *Ankylostomum duodenale*. As a rule the drug is not absorbed and produces no untoward symptoms. In rare cases and when a large quantity is used it acts as a violent irritant to the alimentary tract, giving rise to vomiting and purging which contains blood, and in more severe cases convulsion, coma, dyspnoea and ultimately death from collapse. The purified filicic acid is highly poisonous to mammals, and when given by the mouth acts as a gastro-intestinal irritant. It is very soon absorbed and produces toxic symptoms.

Prescribing hints.—The liquid extract is given in fresh milk or emulsified with fresh mucilage of acacia and flavoured with chloroform water. The patient should lie down after taking the draught, in four equal doses every half-hour. It is best given in the morning on an empty stomach after a purge the previous day. It should be followed 1 to 2 hours later by a saline purgative. Castor oil should not be used either with or after it, as the absorption of the toxic principle is favoured by the presence of oil. The purgative must be a powerful one so as to weaken the head of the worm and loosen its hold upon the intestine. The head must be carefully looked for in the stools, and if it is not found, a second dose of the drug should be given two or three days later so as to expel it. But if more time is allowed the worm grows again and gets strong.

PELLETIERINAE TANNAS. (Pellet. Tann.). Pelletierine Tannate.

Source.—A mixture of the tannates of the alkaloids obtained from the bark of the root and stem of *Punica Granatum*.

Characters.—A light yellow, amorphous powder. Odourless ; taste, astringent. Slightly *soluble* in water, soluble in alcohol (90 p. c.).

Incompatibles.—Alkalies, lime water, metallic salts.

B. P. Dose.—2 to 8 grs. or 0.12 to 0.5 grm.

Pharmacology and Therapeutics

Pelletierine is a valuable anthelmintic for tape-worm. In large doses it causes vomiting and purging. Pelletier-

ine sulphate being soon absorbed by the stomach cannot kill the parasite in the intestine, and in large doses it produces certain constitutional symptoms such as dimness of vision, giddiness, muscular weakness and twitchings, etc. These symptoms do not follow the use of the tannate.

It should be administered on an empty stomach or better still after a dose of castor oil, and a brisk purgative, such as compound jalap powder should follow its use. Only fresh salts are reliable as they deteriorate on keeping. Its use should be preceded by the administration of bicarbonate of sodium in 30 gr. doses three times a day for two days. The decoction of the fresh root-bark is also a valuable taeniafuge.

3. Anthelmintics for hook-worm

CARBONEI TETRACHLORIDUM. (Carbon. Tetrachlor.). CCl_4. —Carbon Tetrachloride may be prepared by the action of chlorine on carbon disulphide.

Characters.—A clear, colourless, volatile liquid ; odour, characterstic ; taste, burning. Not inflammable. In contact with flame decomposes, giving off an acrid odour. Almost *insoluble* in water ; miscible with dehydrated alcohol and solvent ether.

B. P. Dose.—30 to 60 ms. or 2 to 4 mils. (Single dose).

ACTION AND USES

Carbon tetrachloride has been used as a general anaesthetic, but owing to the presence of carbon disulphide as an impurity and the depressant action on the circulation it is twice as toxic as chloroform. It is used as a fire extinguisher, as a rubber and fat solvent, as an ingredient in certain types of paint, and for delousing of clothes. Its use as an anthelmintic has been revived by Maurice Hall for hook-worm and it is a direct poison to *necator*, but is less efficient in *ankylostoma* infections, not more than 30 to 40 p. c. of the latter being cured. *Oxyuris* is also expelled in large numbers. It has been used with success in *T. saginata*, and Barlow recently used it in Fasciolopsis (liver fluke) in China. It is certainly a very effective and safe remedy for hook-worm, the worms being expelled dead and flaccid. It is being replaced by tetrachloroethylene which is equally effective and less toxic.

It passes through the stomach unchanged and probably some absorption takes place in both the small and the large gut. Absorption may be hastened by alcohol and fatty food. The bulk of the drug absorbed is excreted by the lungs.

It is cheap and can be obtained in pure and stable form and is more efficacious than most other remedies. Appearance of toxic symptoms is the only drawback and it is a powerful poison to the liver. In the mass treatment considerable number of deaths occurred in the labour forces in the tea districts. Although some of them are

attributed to ingestion of alcohol either shortly before or after taking the drug, a few cases can only be explained as due to special idiosyncrasy to the drug which cannot be detected by previous examination of the patient.

Toxic effects.—Chief toxic effects are headache, nausea, vomiting, melaena, tremors, tetany, narcosis and convulsion. Cases of fatty degeneration of the liver, kidney and other parenchymatous organs have been observed in post mortem examination.

To avoid toxic symptoms the treatment should not be given to alcoholics, and no food or alcohol should be given shortly before or after treatment. The liability to liver trouble may be avoided by previous use of glucose, 1 oz. daily, for two days. Administration of calcium counteracts the toxic effects when calcium deficiency is suspected. Ammonium chloride also produces the same effect. Choline and methionine may be used.

Contra-indications.—Cirrhosis and other diseases of the liver and patients suffering from calcium deficiency.

Prescribing hints.—The usual dose is 2 to 3 mils (30 to 45 ms.) for adults preferably in divided doses in gelatin capsules, or dissolved in water, although some (Chopra) prefer a single dose for fear of absorption. For children the dose is 2 ms. for each year up to 15 years. As a rule no preliminary purge or rest in bed is required and the patient can be given the anthelmintic and the purgative (sulphate of magnesium) in one dose in the morning and no food is taken for three hours. This is of great importance in mass treatment. Sometimes it is given in combination with oil of chenopodium. This has the advantage of giving both the remedies in smaller doses, and since their effects on the human host are different and independent they produce no harmful effect, on the contrary act as synergists. The best method is to give 3 mils (45 ms.) of carbon tetrachloride and 1 mil (15 ms.) of oil of chenopodium followed by a saline. When round worms are also present, these should be treated first, and one or two weeks should elapse before carbon tetrachloride is given. It forms a uniform emulsion with milk when shaken vigorously, and is an easy and convenient method of administration. Moreover, no burning is felt when administered in this way. It should not be given with oils. The treatment should not be repeated till after a fortnight.

OLEUM CHENOPODII. (Ol. Chenopod.). Oil of Chenopodium. **Syn.—American Wormseed Oil.**

Source.—Oil distilled with steam from the fresh flowering and fruiting plants, excluding roots, of *Chenopodium ambrosioides* var. *anthelminticum*. Contains not less than 65 p. c. w/w of ascaridole, $C_{10}H_{16}O_2$.

Characters.—A colourless, or pale yellow, liquid; odour, characteristic and unpleasant; taste, bitter and burning. *Soluble* in from 3 to 10 volumes of alcohol (70 p. c.).

B. P. Dose.—3 to 15 ms. or 0.2 to 1 mil.

Action and Uses

The oil has a sharp burning taste and causes nausea and sometimes vomiting with a feeling of warmth in the stomach. It is rapidly absorbed from the intestine, which is paralysed, depresses the heart and respiration and causes a fall of blood pressure.

It is one of the most efficient anthelmintics for **ankylostomum duodenale** and also for **round-worm.** It has the

advantage over other anthelmintics of being certain in action. The action is due to the presence of *ascaridole*, but the exact mode of action on the worm is not known. Ordinary doses do not kill the worms but they are only paralysed, and a purgative helps their expulsion.

It has also been used in the treatment of amoebic infection and when administered in the same way as for the treatment of hook-worm, relieves clinical symptoms and causes disappearance of amoebae from the stools. It is reliable for cases resistant to emetine.

Poisoning is rare unless it is given in very large doses. The symptoms are nausea, vomiting, abdominal pain, ringing in the ears, deafness, and in fatal cases coma and convulsion, death taking place from respiratory failure. Different samples vary in their activity and some samples are very unpleasant to take. The preparations obtainable in the market vary a great deal in the irritant properties on the gastro-intestinal tract.

If the dose is carefully regulated and the persons treated are not unduly debilitated, it is a perfectly safe drug.

It is excreted mainly through the lungs and the kidneys. Large doses may cause albuminuria.

Contra-indications.—Pregnancy, as it increases uterine contraction ; advanced cases of heart disease and chronic nephritis. Should be used with caution and in small doses when the heart, liver or the kidneys are disordered.

Prescribing hints.—It is best given in the morning, in doses of 0.5 mil. (8 ms.) each for three doses every hour, either on sugar or in capsules, the patient being kept on light evening meal. The treatment is repeated every three or five days, until the parasites disappear from the stool. The dose may be taken to be 1 min. per year up to 11 years. For healthy adults, 20 to 30 ms. It can also be given in syrup of glucose. The preliminary purgative is not regarded as essential, but an after-purgative removes the drug from the gut, lessens the risk of toxic action and helps to clear out of the bowels accumulated faecal matter and the decomposing worms. The usual purgative is either magnesium sulphate or castor oil. Oils do not increase but lessen toxicity.

The dose for ascaris is 5 to 10 ms. for children on sugar three times a day for two days followed by castor oil.

TETRACHLOROAETHYLENUM. (Tetrachloroaethylen.). Syn. —Perchlorethylene.—Tetrachloroethylene is a colourless mobile liquid ; Odour, characteristic. *Insoluble* in water, soluble in alcohol (90 p. c.) ; miscible with solvent ether and with oils.

B. P. Dose.—15 to 45 ms. or 1 to 3 mils. (Single dose).

ACTION AND USES.—It has the same action as carbon tetrachloride, i. e. valuable in **hook-worm**, but is a little more efficacious and less toxic. It however causes giddiness and drowsiness and the patient should be lying in bed. It should be given in 15 ms. (1 mil.) doses in capsules every hour for three doses daily for three days. Three hours after the last dose on the third day a saline purgative (so-

dium sulphate) should be given. The patient should remain in bed and drink plenty of milk. Alcohol should be avoided.

If ascariasis is also present in the same patient, he should be treated for this first before giving tetrachloroethylene.

It is also useful in **tapeworm,** *T. saginata,* and may be used when filix mas fails, and administered combined with oil of chenopodium.

Hexylresorcinol, B.P.C. Syn.—Caprokol.—In white or yellowish white, needle-shaped crystals, odour, pungent; and a sharp astringent taste. Produces a sensation of numbness when placed on the tongue. Readily *soluble* in alcohol, glycerin, ether, chloroform and vegetable oils.

Dose.—2 to 15 gr. or 0.12 to 1 grm.

Action and Uses.—Hexylresorcinol is a useful anthelminitic for **hookworm, ascaris,** and **thread-worms.** It is rather expensive and is not suitable for mass treatment because of its local irritant effect and fasting for at least twelve hours for treatment to be successful in ankylostomiasis. A single dose removes 90 to 95 p. c. of ascaris, 80 to 85 p. c. of hookworm, and 40 to 50 p. c. of trichuria. Rigid precautions have to be taken before treatment, as it loses its effect when given after food. Half to 1 grm. (7½ to 15 grs.) in capsules should be given on an empty stomach after a purgative the previous evening and no food should be given for four hours after the remedy. For hook-worm, three such courses, at three-day intervals, may be necessary. An after-purgative is not essential.

4. Anthelmintics for thread-worms

These worms inhabit the caecum and therefore rectal injections that are so largely used are not of much value except for removing the worms that have travelled down to the descending colon, sigmoid or rectum. It is probable that these often die out naturally, therefore reinfection of the fingers should be prevented. The female worms wander out of the anus at night and deposit eggs on the surrounding skin causing itching and a desire to scratch; the eggs are thus carried by finger nails to the mouth. Drugs used for hook-worm also help the passage of a large number of thread-worms. The treatment of thread-worm is unsatisfactory, and owing to the toxicity of the drugs used and to prevent reinfection, these patients require careful attention.

VIOLA CRYSTALLINA. Syn.—Medicinal Gentian Violet; Methylrosaniline Chloride.—Crystal Violet is the hydrochloride of hexamethylpararosaniline.

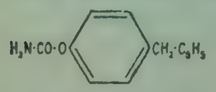
Characters.—Greenish-bronze crystals or powder: odourless or nearly so. Soluble in about 150 parts of water, very soluble in alcohol (90 p. c.), in 30 parts of glycerin, soluble in chloroform.

Action and Uses.—Crystal violet is a valuable anthelmintic for thread-worms. The usual dose for adults is 1 gr. (60 mg.) three times a day before meals for eight days, followed by a rest period of seven days. It may again be

used for another eight days. For children the dose is $\frac{1}{6}$ gr. (10 mg.) a day for each year of apparent age. The total dose being divided into three doses. These should be given in enetric coated tablets or pills. It is also used in *Strongiloides* infestation in 1 gr. doses three times a day after meals for ten to fifteen days.

Contraindications.—When associated with round worm infestation, cardiac, hepatic and renal disease, alcoholics, and those suffering from diseases of the gastro-intestinal tract.

DIPHENANUM. Syn.—Butolan.—Diphenan is *p*-benzylphenylcarbamate.—A white or very pale cream crystalline powder; odourless; tasteless. Almost *insoluble* in water ; sparingly soluble in alcohol (90 p. c.).



B. P. Dose.—8 to 15 grs. or 0.5 to 1 grm.

ACTION AND USES.—It is an anthelmintic for thread-worms (oxyuris) and is also useful in certain phases of *trichinosis.* It acts directly on the worms causing great contraction followed by death within five minutes. It is administered in tablets of 8 grs. (0.5 grm.) for adults three times daily for one week followed by a dose of castor oil. The treatment may be repeated after an interval of 8 or 9 days. For children over ten years the dose is same, but for younger children the dose is proportionately smaller. The rectum should also be daily washed with infusion of quassia.

Hexylresorcinol.—*Dose,* 1 grm. (15 grs.) for adults and children over 10 years ; below 10 years, 0.1 grm. ($1\frac{1}{2}$ gr.) for each year of age. Given in hard gelatin capsules. This should be followed by soap water enema, followed by another enema of 0.1 p.c. hexylresorcinol and kept for 15 minutes.

Phenothiazine, B.P.C. Syn.—Thiodiphenylamine: Phenovis.—A lemon yellow thiazine dye. Most effective but considerable risk in treatment, therefore justifiable only when other methods have failed. Toxic effects are photosensitisation of the skin, toxic hepatitis and haemolytic anaemia. It is not necessary to restrict food. and should be *given daily for seven days.* The dose for children from five to ten years is 15 grs. (1 grm.) a day; below five years 8 grs. (0.5 grm.) followed by a saline at the conclusion of the course.

It is largely used in veterinary practice against ascaridae and strongilus.

5. Anthelmintics for filarial infection

Hetrazan. (Not official).—It is 1-diethylcarbamyl-4-methylpiperazine hydrochloride. A synthetic piperazine derivative introduced for the treatment of filariasis due to *Wucheraria bancrofti* infection. The mechanism of its action is not known but it has a remarkable lethal effect on the microfilaria which disappears within 48 to 72 hours of its administration. It has been suggested that it acts by sensitizing the microfilariae for phagocytosis by the reticuloendothelial system. Treatment consists of giving 2 mg. (1/30 gr.) daily per kg. of body weight, three times a day orally after food, for a period lasting from 7 to 21 days. Apart from its effects on the embroys it

is possible that it also acts on the parent worms as it causes nodular swellings in some patients caused by the dead or dying worms. Slight nausea, anorexia, malaise, general weakness, etc. are sometimes observed but these pass off soon. It has also been found efficacious in *Onchocerca volvulus*.

Dose.—0.5 to 2 mg. (1/120 to 1/30 gr.) per kg. of body weight.

GROUP XIV

DRUGS ACTING ON THE KIDNEYS

The kidneys help to maintain the normal composition of the fluids of the body by separating from the blood the waste products of nitrogenous metabolism and other organic and inorganic constituents which are present in excess and which are not required by the body or cannot be metabolised. They help to preserve the alkaline reserve of the body by eliminating the non-volatile acids formed in the metabolic process, the volatile acids (CO_2) being excreted by the lungs. They help to keep the volume of blood and generally the fluid contents of the body as a whole at a constant level, and also maintain the osmotic pressure at a definite level by excreting the excess of water as occasion demands.

Since all substances eliminated by the kidneys are kept in solution it is necessary that sufficient water should be available from the body. It is not possible to reduce the normal water content of the blood, and in order that diuresis may occur there must be an excess of water however small in the blood, *i. e.* hydraemia must be present. The hydraemia however is only temporary, for the excess of water passes from the vessels into the different tissues until the pressure becomes equal.

The fact that urea, uric acid, pigments, salts and water, which constitute the bulk of the urine are not manufactured by the kidneys, makes these organs of special interest to the pharamacologist. Inasmuch as digestion, assimilation, metabolism and circulation affect the activity of the kidneys, the condition of the urine furnishes a key as to the manner in which the different organs are performing their respective functions.

A healthy man passes about fifty ounces of urine daily, which is acid in reaction and contains about 2.2 p. c. of urea; whereas the blood is alkaline in reaction and contains only 0.05 to 0.1 p. c. of urea. It is evident therefore that considerable change of the fluid takes place during its passage through the kidneys before it reaches the ureters.

The different parts of the kidneys perform different functions. The glomerulus with the tubules form the renal unit, for convenience described as the *nephron*. Each kidney contains about one million such nephron. The *glomerulus* helps the passage from the blood to the

tubules of a large quantity of fluid of alkaline reaction containing urea, chloride, sulphate, phosphate, etc. The fluid undergoes further changes in the *convoluted tubules*, where its reaction becomes acid, and urea, uric acid and other nitrogenous substances are added by process of excretion, and the urine becomes more concentrated by the reabsorption of some of the water. Cushny holds that glomeruli act as ultra-filters and filter off a fluid containing all the non-colloidal constituents of the plasma, *i. e.* all the abnormal constituents and most drugs.

In order that the kidneys may function properly they must have ample supply of oxygen, and this has been rendered possible by an abundant blood supply. The blood flow through the human kidneys daily is about 170 litres.

The composition of the blood itself exerts considerable influence in the production of diuresis. The plasma proteins by their tendency to bind water, exert an oncotic pressure which resists filtration of fluid. When the plasma proteins fall below a certain level increased transudation must result. Moreover, the water-binding properties of the colloids are influenced by certain crystalloids, and possibly by some of the hormones. Increased alkalinity within clinical limits tends to favour water retention, while acids tend to diuresis.

Other things being equal, the greater part of the watery portion of the urine is excreted from the glomeruli, and this depends upon the glomerular pressure and the amount of blood flowing through it. If the blood flows through the glomerulus at a low pressure, due to resistance to efferent vessels, or if there is any obstruction to renal veins, the secretion of urine is diminished, although the glomerular pressure may be high in the latter case. It is evident therefore that diuresis occurs only when there is a continuous and rapid flow of blood under certain amount of pressure through the glomerulus. The rate of blood flow through the kidneys depends upon the general arterial pressure, the condition of the kidney vessels, and the pressure in the veins. The capillary system of the glomerulus supplied by the vasa afferentia and that of the tubules supplied by the vasa efferentia are antagonistic to each other. When the vasa afferentia dilate and vessels of the tubules contract, the pressure and the flow in the glomeruli increase, whilst that to the tubules will be less and *vice versa*.

It must not be supposed that the kidneys simply act as filters, inasmuch as they interpose a barrier in the way of excretion for any substance in the blood which can be of use to the tissues ; and if the amount of this substance in circulation does not exceed a certain limit, the kidneys do not excrete it. This rule applies to sugar, salt, haemo-

globin and biliary constituents, and like water are retained in the blood up to a certain limit by a corresponding regulation of their reabsorption by the tubules. Thus sugar is not excreted unless its concentration is above 0.18 p. c. in the blood, and only when this threshold is exceeded that these substances are excreted in the urine. These substances are termed *threshold substances.* On the other hand no such barrier exists to purely waste products, such as urea, uric acid, etc., and these are termed *no threshold substances.*

The mechanism of diuresis is still unsettled, although it is possible that the secretion of urine is controlled by chemical stimuli. Various foreign substances, even the normal constituents of blood, when present in sufficient concentration, stimulate in some way the kidney cells. It is probable that the increased amount of urine which follows the improvement of kidney circulation may be due to the presence of a greater amount of chemical stimuli and other substances which pass through the organ.

Diuretics are drugs which increase the flow of urine. Increased urine may represent an increased intake of water or may be the result of removal of fluid from the tissues.

Diuretics may be classified as follows :—

I. *Acting by increasing the number of glomeruli functioning at a given time.*—Although there are about two million glomeruli in the human kidneys, Richards and his associates have shown that all of them do not function at the same time, since the capillaries dilate only in those that are active, the rest remain closed. Each glomerulus together with its tubules forms a renal unit, and diuresis depends upon the number of glomeruli functioning at a given time. **Caffeine** and **urea** are supposed to act in this way, thus **increasing the filtering surface.**

II. *Acting by increasing the flow of blood through the kidney or by raising the glomerular arterial pressure.*—The secretion of urine is largely proportional to the glomerular pressure and the rapidity with which the blood flows through the kidneys. Thus when there is congestion of the renal veins as in failure of compensation, the secretion is diminished, and improvement of circulation by increasing the action of heart produces diuresis, *e. g.* by drugs of the digitalis group, **caffeine, theophylline, theobromine,** etc. They are known as **cardio-vascular diuretics.** Dilatation of renal vessels as by the use of **spirit of nitrous ether** also causes diuresis. Similarly, by constricting efferent glomerular veins the pressure in the glomerulus may be increased, as by **pituitary extract** and **adrenaline in minute doses.**

Accumulation of fluid in the abdominal cavity mechanically hinders the outflow through the renal vessels, and removal of fluid, either by tapping or by purgation, removes venous stasis and produces **diuresis.**

The glomerular pressure may also be increased by making the blood hydraemic, *i.e.* by reducing the concentration of plasma protein (1) by drinking large amount of water, and (2) by injecting **normal saline solution,** either subcutaneously, intravenously, or into the **rectum.**

III. *Acting by causing acidosis.*—It has been found that large doses of **ammonium chloride** and **calcium chloride** cause reduction of the alkaline reserve of the plasma and act as diuretics. They increase the non-colloidal constituents of the blood plasma and by reducing the concentration of the plasma proteins help diuresis.

IV. *Acting locally on the kidneys.*—Moderate irritation dilates the renal arterioles and raises the glomerular pressure, while the pressure in the arterial system generally and the resistance in the renal veins, remain unchanged. They stimulate the kidney cells and produce diuresis either by increasing the tubular secretion or by diminishing tubular reabsorption. These are also known as *irritant diuretics.* Except caffeine and its allies most of them irritate the kidney cells causing congestion and even nephritis when given in large doses. They are :—

(*a*) Glycosides ; these are related to the aromatic series, **broom** (scoparin).

(*b*) **Acids, alkalies** and some salts, **caffeine, theobromine** and other **purine derivatives, calomel, mersalyl, novasurol.**

(*c*) *Certain volatile oils.*—**Buchu,** oils of **juniper** and **sandal wood.**

V. *Acting by salt action.*—These act by lessening viscidity of the blood, thereby increase the filtrability and the glomerular pressure. They also prevent reabsorption from the tubules. The effect is proportional to the osmotic pressure which they exert. **Water, urea, acetate and citrate of ammonium, salts and sugar** act in this way.

Therapeutics.—The diuretics are indicated to remove either water or solids from the body, and have the following uses :—

(1) Cardiac and pulmonary disorders where the quantity of urine is diminished, or there is chance of dropsy.

(2) To hasten the elimination of waste products or poisonous materials circulating in the blood.

(3) Conditions where there is accumulation of fluid in some natural cavities of the body, as in ascites and pleurisy.

(4) To dilute the urine in inflammation of the bladder and urethra to make it less irritating, and in cases with a tendency to formation of calculi or deposition of solids.

Antidiuretics.—Adrenaline in the first stage, when the renal vessels are constricted, diminishes the secretion of urine, and pituitary extract in later stage also diminishes the secretion of urine and both are *antidiuretics.* Urine is diminished after saline and hydragogue purgatives and during the toxic stage of digitalis.

Reaction of the urine.—The normal reaction of human urine is slightly acid with a *p*H range from 5.12 to 7.46, with an average of 6.03. During digestion when the gastric secretion is increased and during fasting the acidity becomes less.

Drugs which increase acidity of the urine.—The urine can be made acid by the use of acid salts, like acid sodium phosphate, or by the use of ammonium or calcium chloride, mandelic acid, benzoic acid, boric acid and salicylic acid. The reaction becomes altered or may be highly acid by the use of mineral acids, but in practical therapeutics their usefulness is limited owing to their local irritant effect.

Drugs which make urine alkaline.—We have however more powerful means of making urine alkaline. The salts of sodium, potassium, and lithium which are oxidised in the blood as carbonates and are eliminated as such by the kidneys render the urine alkaline.

Those salts of ammonium that are eliminated as urea have very little effect in making the urine alkaline.

Urinary lithontriptics.—These are remedies employed for dissolving any concretions or calculi formed in the urinary tract or for preventing the deposition of solids from the urine. Alkalies are

used in uric acid and oxalate of lime calculi. Benzoates are used when the urine is undergoing alkaline decomposition and phosphatic calculi are liable to be formed.

Class A : Diuretics

Source. Distil potable water from a neutral glass or metal still fitted with an
Acetate. Mersalyl (see **mercury**), **Urea, Oil of Juniper, Scoparium, Apocynum** (see
page ...), **Spiritus Aetheris Nitrosi, Digitalis** and its allies (see page 284), **Acetate**
... collect the remainder in a sterilised neutral glass container. Close the
container to exclude bacteria, and sterilise immediately by heating in autoclave.

AQUA DESTILLATA

(Aq. Dest.)

Source and Characters.—Distilled Water is prepared by the distillation of potable water. A clear, colourless, odourless and tasteless liquid.

Official Preparation

1. **Unguentum Aquosum.—Water 50 p. c.**

Aqua pro Injectione. (Aq. pro. Inj.).—Water for Injection.

Source. Distil potable water from a neutral glass or metal still fitted with an efficient device for preventing entrainment. Reject the first portion of the distillate and collect the remainder in a sterilised neutral glass container. Close the container to exclude bacteria, and sterilise immediately by heating in autoclave.

Body Water and Water Balance

Water is the most important constituent of the body and forms about 64 to 90 p.c. of the body weight, and the daily loss from the system is about 100 ozs. This body water is largely derived from food and extra water drunk. It is necessary to compensate for the losses caused by the excretory organs and for the repair of the various fluids, and of the solid organs of the body into whose composition it enters. The amount of water taken as drinks is about 1300 mils (45 ozs.) and that with food is 1000 mils (35 ozs.) and that produced by metabolism of food is 300 mils (10 ozs.). Under ordinary circumstances the intake and output are balanced. Of this total intake of 2600 mils (90 ozs.), 1300 mils is excreted by the urine, 1000 mils by respiration and invisible perspiration, and 300 mils by the faeces. In warm countries the amount of water taken is much larger as also the amount lost by perspiration which may be several litres. The demand for water is indicated by thirst and an insufficient supply will lead to disturbances of circulation and the heat regulating mechanism and to retention of the products of metabolism.

The maintenance of water balance is of prime importance for the physiological well-being of the organism and the kidneys play the most important part in maintaining this balance. Water is constantly undergoing shifts in the body to meet the physiological demands of the organism and exists as (*a*) *extra cellular water*, which includes plasma water and water in the interstitial fluid, and (*b*) *intracellular water*, which forms about 50 p.c. of the total body weight and is the water contained in all body

cells. The plasma proteins play an important part in th maintenance of blood volume and thus determine the wat content in the tissues. Being composed of large particle they cannot diffuse through the capillary wall. The extr cellular fluid contains sodium chloride in isotonic solutio therefore 9 grm. of sodium chloride will hold about 1 litr of water in the interstitial fluid to maintain proper osmoti balance. Adrenal cortex is essential for the maintenanc of water balance and loss of sodium chloride and retentio of potassium, as happens in Addison's disease, will caus loss of water to compensate for the diminished osmot pressure. Potassium and sodium salts, therefore, ar valuable agents to effect a favourable shift of water balanc in disease.

PHARMACOLOGY OF WATER

Externally.—Water is not absorbed through the un broken skin, although the epithelial cells slowly absorb i and eventually swell up. Application of cold water cause constriction of the cutaneous vessels and stops perspira tion, while hot water dilates the vessels, helps radiation o heat, increases perspiration and lowers temperature. Col sponging reduces temperature by abstraction of heat Application of cold water to the body reflexly stimulate coughing and increases inspiratory efforts.

Internally.—Water is very slowly absorbed from th stomach, the normal epithelium of the stomach is scarcel permeable to water. It passes rapidly into the duodenun and is absorbed from the intestine. A large portion i passed out with the stool. When taken mixed with alcoho or carbon dioxide (aerated water) it is absorbed mor freely by the stomach.

Taken in moderation with meals it increases salivary gastric, biliary and pancreatic secretions and helps diges tion. As it helps better absorption of foods, less materia is left in the gut for putrefactive bacteria. Taken i large doses it causes vomiting, while hot water slowl sipped is a valuable gastric sedative and antiemetic.

Kidneys and skin.—Drinking large quantities of wate causes hydraemia and acts as diuretic. It is a commo experience to observe increased perspiration and urin when more water is given, and this is in proportion to th amount of water consumed. In fact water is the onl diuretic and almost all diuretics act by supplying th kidney more water, *i.e.* by making the blood passin through the kidney vessels hydraemic. The excretion o excess of water in unanaesthetised animals is controlle by the pituitary and the hypothalamus. Drinking of wate is accompanied by increased flow of blood and lymph whic washes out from the body effete materials and toxins

diuresis also helps to wash out the pelves of the kidneys of the infective matter and helps removal of gravel.

Metabolism.—Water flushes the salts and different products of metabolism out of the system. During its passage through the blood and tissues pure water decreases osmotic pressure, and by internal exchange of salt and water between the blood and tissues, and by eliminating the excess material by the kidneys it helps to keep the composition of the blood constant. Nitrogen elimination is increased chiefly in the form of urea, and the sulphates and phosphates are also increased.

Therapeutics of Water

Externally.—Besides its uses already discussed in pages 39-41, water, in the form of ice, or constantly changed through a Leiter's coil, is useful in subduing many acute inflammatory diseases, such as meningitis, cerebritis, synovitis, sprains, etc. It contracts not only the superficial blood-vessels, but also those of the internal organs by reflex action. On the same principle, a local application of ice to the surface arrests internal haemorrhages, such as epistaxis, haematemesis, etc. A smart sprinkling of cold water on the face restores consciousness in hysteria, fainting and narcotic poisoning. The same plan may be adopted in reviving still-born infants.

Internally.—The sucking of ice allays thirst, vomiting and hiccough. A glass of hot water before meals soothes the irritable condition of the stomach in gastritis, gastrodynia and gastric ulcer. A glass of cold water taken immediately on rising from bed helps the bowels to act. The swallowing of ice arrests haematemesis. Copious draughts of water help to wash out minute deposits of urinary gravel. If it is a uric acid calculus, drinking of distilled water diminishes the tendency to deposition. As a diuretic Glaessner advocates the oral administration of distilled water for uraemia, hypertension without arteriosclerosis, and urinary lithiasis. Large draughts of water given between meals may arrest the formation of gallstones by liquefying the bile. As an *emetic*, warm water should not be given in quantities sufficient to over-distend the stomach, as this may paralyse the muscles and thereby impede rather than promote vomiting. Half to one pint at a time is enough for the purpose. In oedema water is only a safe diuretic when the salt intake is limited. On the other hand its restriction is helpful in acute nephritis and cardiac oedema when the renal circulation fails to deal with normal quantities of fluid. The intake of water should be gradually increased as the kidneys show evidence of being able to deal with it.

Aqua pro Injectione or Water for Injection is used for

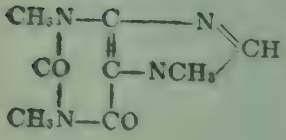
making solutions for intravenous injection. It should b noted that a large volume of sterilised water given intra venously causes laking of blood and therefore should b avoided and isotonic saline should be used.

Good tap water though contains a trace of organi matter will if introduced intravenously may cause alarm ing reaction which takes the form of rise of temperature rigor and leucocytosis. A water which has been re distilled with an efficient device for preventing entrain ment does not give rise to these reactions. The unidenti fied nitrogen-containing organic compounds which giv rise to these reactions are termed "pyrogens", and wate for intravenous injection must be *pyrogen free.*

Water poisoning.—By administering large volumes of water b the mouth it was possible to produce water poisoning in dogs. Unde normal conditions it is not possible to produce water poisoning i man unless extract of pituitary is also simultaneously administere which by virtue of the antidiuretic principle helps retention of wate in the body. The symptoms of water intoxication are nausea vomiting, headache and dizziness which may lead to coma, convul sion and death. It may occur when the excretion of water ceases but the patient keeps on drinking in case of kidney disease, and when there is an excess of antidiuretic principle of posterio **pituitary.**

CAFFEINA

Caffeine. (Caffein.). $C_8H_{10}N_4O_2,H_2O$



Syn.—Theine ; Guaranine.

Source.—An alkaloid obtained from the dried leaves of *Camellia sinensis*, o from certain other plants ; or may b prepared synthetically. It is 1 : 3 : 7 trimethylxanthine.

Characters.—Colourless, silky needles : odourless : taste, bitter. *Solubility.*— 1 in 80 of cold water, more in alcohol (90 p. c.), and in chloroform. The aqueou solution is neutral.

Incompatibles.—Tannic acid, potassium iodide and mercurial salts.

B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

CAFFEINA ET SODII BENZOAS. (Caffein. et Sod. Benz.).

Source.—Caffeine and Sodium Benzoate is prepared by mixin caffeine with an equal weight of sodium benzoate. Contains 47 to 5 p. c. of anhydrous caffeine, and 50 to 53 p. c. sodium benzoate.

Characters.—A white powder : odourless : taste, slightly bitter. *Soluble* in part of warm water ; completely in 4 parts of water, slightly in alcohol (90 p. c.)

B. P. Dose.—5 to 15 grs. or 0.3 to 1 grm. ; or 2 to 5 grs. or 0.12 to 0.3 grm (by subcutaneous injection).

Official Preparation

1. **Injectio Caffeinae et Sodii Benzoatis.—B. P. Dose.—2 to 5 grs. or 0.12 t 0.3 grm.** By subcutaneous injection. When no dose is stated, 3¾ gr. (0.25 grm. in 15 ms. should be dispensed. N. B. The label should state the strength of caffein and sodium benzoate in suitable dose-volume, and the name and percentage of an added bacteriostatic.

Non-official Preparations

1. **Migrainine.** *Syn.—Antipyrin Caffeine-citricum.*—Soluble in water : con tains 9 p. c. caffeine, 1 p. c. citric acid, and 90 p. c. phenazone. In *headache*, bu causes sleeplessness. *Dose.*—**8 to 15 grs. or 0.5 to 1 grm.**

2. **Caffeine et Sodii Salicylas, B.P.C.** Evaporate to dryness Caffeine 5, Sod Salicylas 5, Water 20. A white amorphous powder containing 47 to 50 p.c. of caffeine Acts like digitalis, but more rapid. *Dose.*—5 to 15 grs. or 0.3 to 1 grm. by mouth **2 to 5 grs. or 0.12 to 0.3 grm. hypodermically.**

3. **Caffeinae Citras, B.P.C.**—White inodorous powder with an acid reaction. Soluble in 32 parts of water. *Dose.*—2 to 10 grs. or 0.12 to 0.6 grm.

4. **Caffeina et Sodii Iodidum, B.P.C.** *Syn.*—*Sodium Caffeine Iodide.* A white powder, slightly soluble in cold water and freely in warm water. Contains 56 p.c. caffeine. A valuable diuretic in *cardiac dropsy* and *pleurisy*. Useful in *asthma*. *Dose.*—2 to 10 grs. or 0.12 to 0.6 grm.

PHARMACOLOGY

The drugs belonging to this group are called purine derivatives because they are derived from xanthine, one of the purine bases.

Internally.—Caffeine has three important actions, *viz.*, (1) it is a diuretic; (2) it is a cerebral stimulant and excites the higher nervous centres; (3) it stimulates the heart and dilates coronary vessels.

Heart and circulation.—In medicinal doses it slows the pulse from **stimulation of the inhibitory centre** and increased vagus excitability. Frequently however no change in the pulse-rate is observed. It increases the absolute strength of the heart and enables it to overcome greater resistance. The systole is increased but it does not increase the diastolic relaxation, which may be reduced, the contraction of the heart-muscle antagonises relaxation and the filling of the heart during diastole (see fig. 26). In some cases the stimulation of the heart is pronounced possibly due to increased blood flow through the dilated coronary arteries. In toxic doses the pulse becomes very frequent, irregular and intermittent, and at last the heart stops in systole. These effects are largely due to the direct action of the drug on the cardiac muscle, chiefly the nodal tissue and the bundle of His, and partly on the cardio-inhibitory centre.

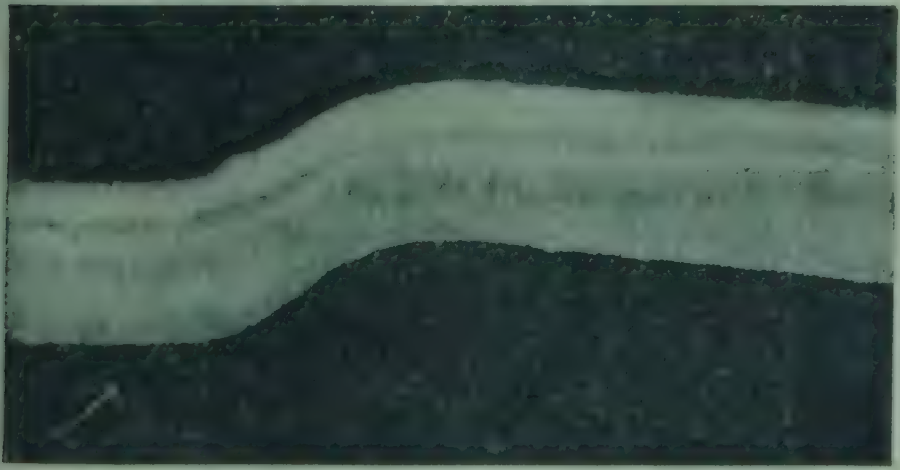


Fig. 26.—Effect of Caffeine on Isolated Rabbit's Heart

At point of arrow a small amount of caffeine was added to the perfused fluid. Note increased tone of the heart. Systole is increased with imperfect relaxation of diastole.

The vaso-constrictor centre is moderately stimulated and this combined with increased output of the heart will tend to cause a rise of blood pressure ; on the other hand there is peripheral vaso-dilatation which overcomes the effect of constriction. In fact caffeine causes a rise of blood pressure at the beginning but this is offset (generally after 20 minutes) by fall of pressure due to peripheral vaso-dilatation through direct action on the walls of the vessels. But this fall in ordinary therapeutic doses is not of much consequence as it is not ordinarily below normal.

An injection of caffeine and sodium benzoate usually causes a slight slowing of the pulse without any appreciable effect on the arterial pressure. But this often induces undesirable nervous symptoms which precludes it from being used repeatedly without risk of over-stimulating the brain and cord. It has no effect on arteries not under control of the vaso-constrictor centre. The coronary arteries are dilated.

Respiration.—In therapeutic doses given by the mouth the respiration is moderately stimulated, sometimes however it is scarcely affected unless cardiac dyspnoea is improved by the circulatory effect. The respiration is definitely stimulated when given as an injection.

Temperature is not affected by small doses but is increased by large doses.

Nervous system.—Caffeine stimulates the central nervous system, and in small doses acts entirely on the higher psychical centres, this being the only part really affected, hence there is mental exhilaration and removal of fatigue and languor and a state of drowsiness and inattention becomes one of wakefulness and brightness and activity. It decreases fatigue and increases the amount of physical work due to its action on the motor area of the brain. It has been shown that there is an increase in both the rapidity and accuracy of purely intellectual processes ; but caffeine has no effect on those forms of cerebral activity which require a combination of mental processes with physical co-ordination. The perceptions become more acute, pain is more keenly felt, and the sense of touch becomes more discriminating. Caffeine therefore is a **cerebral stimulant.** It increases all conditional reflexes and diminishes all inhibitory processes. In larger doses it stimulates the motor area as evidenced by restlessness, wakefulness, ringing in the ears, delirium and tremors.

Medulla and Cord.—The **respiratory centre** is powerfully **stimulated,** and there is general vaso-constriction due to slight stimulation of the **vaso-constrictor** centre. The **vagal centre** is also stimulated but this is of minor importance since this effect is overshadowed by its action on the cardiac muscle. The motor cells of the cord are also stimu-

lated with acceleration of the passage of impulses like strychnine, but more mildly. It, therefore, increases the reflex activity and improves the tone of muscle.

Muscle.—Its action is well marked on the skeletal muscles. A moderate dose will directly increase the strength and irritability of the muscle ; so that a weak stimulus will cause contraction and the total amount of work done before exhaustion sets in is increased. Considering the universal use of beverages containing caffeine it is of practical importance to know that as a result of human experiments with ergograph the increase in muscular power is not followed by a compensatory depression.

Metabolism.—The effect of caffeine on metabolism is not clear. It increases the excretion of xanthine and urea, consumption of oxygen and elimination of CO_2. There is some rise of temperature due to increased muscular activity and effects on the nervous system.

Kidneys.—Caffeine is a powerful **diuretic** and it has been found that under its use the kidney vessels are dilated while causing general vaso-constriction thus increasing the filtration pressure in the renal vessels. Verney* asserts that it acts by increasing the number of glomeruli functioning thus increasing the filtration surface. The extent of diuresis varies with the amount of water in the body ; and the urine is of low specific gravity, the urinary solids are less augmented than the watery portion of the urine, *i.e.* the diuresis depends upon the amount of filtration fluid available in the body and becomes less when the accumulated fluid is eliminated and the body becomes relatively "dry." Diuresis depends upon an increase of the non-colloidal constituents of the blood which by reducing the osmotic resistance to filtration allows more fluid to pass through the glomeruli into the tubules. It has been found that on a salt-free diet sodium chloride almost disappears from the urine as it is reabsorbed to maintain an adequate concentration of salt in the blood. If however caffeine is administered the salt reappears in the urine. It has therefore been suggested that caffeine *interferes with the reabsorption of salt* by the tubules, as a result of which more salt remains in the tubules which exerts an osmotic pressure and hinders reabsorption of fluids. 2

As a diuretic caffeine is inferior to theobromine and theophylline, and of these theophylline acts more powerfully on the kidney. Caffeine however does not injure the kidneys when used for a prolonged period even in large doses. It has therefore the advantage over other diuretics and causes no further damage to the kidneys when used in renal disorder.

* *Quarterly Journal of Pharmacology*, 1928.

Absorption and clearance.—Caffeine is rapidly and completely absorbed, only a very small percentage being eliminated in the urine, and none appears in the stool even when given in large doses. About 80 p.c. is completely oxidised into urea, the rest being excreted in the urine as di- and mono-methylxanthine. When used for a long time a certain degree of tolerance is produced so that diuresis is not so marked after some time.

Acute toxic action.—Burning in the throat, thirst, gastro-intestinal pain, violent vomiting and purging, giddiness, tremors in the extremities; free diuresis, clear intellect were observed in a case of poisoning by 60 grs. of the citrate; recovery took place under the use of nitroglycerin. As a rule very few fatal cases occur as a result of caffeine poisoning; possibly the fatal dose is very large, but when taken in doses above 1 grm. it produces alarming symptoms. Even therapeutic doses may give rise to unpleasant side effects.

Treatment generally consists in giving bromides, alcohol and morphine.

THERAPEUTICS

Internally. **Heart.**—As a *cardiac stimulant* caffeine is chiefly used as an emergency drug and should not be repeated frequently. It is therefore usefully employed to revive the heart in cardiac failure in chronic heart diseases, and may be given either with digitalis or alternating with it. Given hypodermically it is valuable in acute **heart failure in febrile diseases,** *e.g.* in pneumonia, oedema of the lungs, etc. As it does not possess the permanent tonic action of digitalis, it cannot replace that drug, but may with advantage be used as an adjuvant when a greater effect is desired. It is of signal service in cardiac dropsy, specially when combined with digitalis. It may be used to strengthen the heart in many acute diseases, such as pneumonia, fevers, etc. Effective therapeutic doses however are liable to produce certain side effects, *viz.*, palpitation, vertigo, nausea, vomiting, restlessness, sleeplessness, and sometimes delirium, when mental rest and sleep may be of the highest value to the patient. These effects are more apt to occur in patients with interstitial nephritis.

Respiration.—As an **analeptic to stimulate respiration** caffeine may be used in oedema of the lungs and failure of respiration, *e.g.* in alcohol and morphine and other narcotic poisoning. Hot black coffee is largely used in narcotic poisoning to stimulate the respiratory centre. Sometimes it relieves the paroxysms of asthma, possibly by dilating the bronchial muscle, but the effect is weaker than atropine or adrenaline.

Nervous system.—In migraine caffeine or the citrate, in combination with aspirin, phenacetin, etc., to assist their action and to prevent their depressing effect on the heart, is sometimes useful. Owing to its action on the central nervous system it is used in nervous exhaustion

and as it stimulates the brain and respiratory centre it is used in alcoholic poisoning.

Kidneys.—Caffeine is an uncertain diuretic and has now been superseded by diuretin, agurin and theophylline, but these tend to cause gastric irritation, nausea and vomiting. It is largely used in cases of **cardiac dropsies,** and is of value as a preliminary to digitalis treatment. Its value is not so certain in renal and hepatic dropsies. In chronic parenchymatous nephritis there is as a rule very little response, while in chronic interstitial nephritis it usually gives better results. Many patients get habituated to its use and its **diuretic action is entirely lost on** them after a week or so. On account of its stimulating action upon the kidney cells caffeine *should not be given in acute nephritis.*

Prescribing hints.—Caffeine is usually given alone but it may be combined with other drugs, such as strychnine or digitalis as they mutually help each other, or it may be exhibited alternately with digitalis. As an emergency drug caffeine sodium benzoate should be used hypodermically. When caffeine is used as a circulatory stimulant it stimulates the cerebral cortex, and a few doses may cause excitable nervous condition with wakefulness when sleep may be of the greatest value to the patient. As it stimulates perception it may increase the patient's suffering.

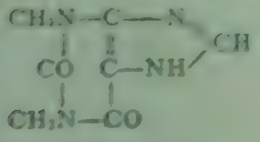
THEOBROMINA ET SODII SALICYLAS

(Theobrom. et Sod. Salicyl.)

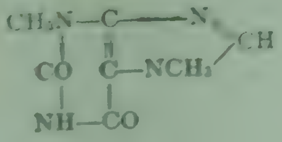
Syn.—Diuretin.—Theobromine and Sodium Salicylate is a mixture of sodium theobromine and sodium salicylate in approximately equimolecular proportions. Contains not less than 46 p.c. of theobromine, 41 p.c. of sodium salicylate, and not more than 6.9 p.c. of sodium, Na, additional to that contained in the sodium salicylate.

Characters.—A white, amorphous powder. No odour; taste, sweetish and alkaline. *Solubility*.—In equal parts of water. Insoluble in alcohol (90 p.c.), in solvent ether and in chloroform.

B. P. Dose.—10 to 20 grs. or 0.6 to 1.2 grms.



Theophylline



Theobromine

THEOPHYLLINA. (Theophyll.). Theophylline. **Syn.**—Theocin.

Source.—It is 1:3-dimethylxanthine, an alkaloid obtained from the dried leaves of *Camellia sinensis*, or prepared synthetically.

Characters.—A white, crystalline powder: odourless: taste, bitter. *Soluble* in [illegible] parts of water at [illegible] °C.; more in hot water; in [illegible] parts of alcohol (95 p.c.); [illegible] soluble in solvent ether.

B. P. Dose.—1 to 3 grs. or 60 to 200 mg.

Enters into.—Injectio Mersalyli.

Theophyllina et Sodii Acetas. (Theophyll. et Sod. Acet.). **Syn.**—Theocin Sodium Acetate.—Theophylline and Sodium Acetate is a hydrated mixture of sodium theophylline and sodium acetate in approximately equimolecular proportions. Contains not less than [illegible] p.c. of anhydrous theophylline.

Characters.—A white, crystalline powder ; odourless ; taste, bitter. *Soluble* in 25 parts of water, insoluble in alcohol (90 p. c.), in solvent ether and in chloroform. Solution alkaline to litmus.
B. P. Dose.—2 to 5 grs. or 0.12 to 0.3 grm.

Theophyllina cum Aethylenediamina. (Theophyll. c. Aethylenediam.). Syn.—Euphyllin ; Cardophylin ; Aminophylline.—Theophylline with Ethylenediamine contains from 71.5 to 78.5 p. c. of anhydrous theophylline and from 11.8 to 13.2 p. c. of ethylenediamine.

Characters.—White or yellowish-white granules ; odour, faintly ammoniacal ; taste, bitter. *Soluble* in about 5 parts of water, insoluble in dehydrated alcohol and in solvent ether.
B. P. Dose.—1½ to 8 grs. or 0.1 to 0.5 grm.

Official Preparations

1. **Injectio Theophyllinae cum Aethylenediamina.** *Syn.—Aminophylline Injection.*—**B. P. Dose.—1½ to 8 grs. or 0.1 to 0.5 grm.** by intravenous or intramuscular injection. N. B. When no strength of the injection is given, 4 **grs. (0.25 grm.)** in **150 ms. (10 ml.)**, for intravenous injection, and 8 **grs. (0.5 grm.)** in **30 ms. (2 ml.)** for intramuscular injection, shall be supplied.
2. **Tabellae Theophyllinae cum Aethylenediamina.** *Syn.—Tablets of Aminophylline.*—**B. P. Dose.—1½ to 8.gr. or 0.1 to 0.5 grm.** N.B. When the quantity contained in a tablet is not stated, 0.1 grm. (1½ gr.) tablets shall be supplied.

Non-official Preparations of Theobromine and Allied Purine Derivatives

1. **Theobromina, B.P.C.** *Syn.—Dimethylxanthine.*—Isomeric with theophylline. an alkaloid obtained from the seeds of Theobroma cacao. *Dose.*—5 to 10 grs. or 0.3 to 0.6 grm.
2. **Theobromina et Sodii Acetas, U. S. P.** *Syn.—Agurin.*—A deliquescent powder, easily soluble 1 in 2 of water. *Dose.*—7½ grs. or 0.5 grm.
3. **Theobromine Calcium Salicylate.** *Syn.—Calcium Diuretin* ; *Theocalcine.*—Contains 48 p.c. theobromine and 11 p.c. calcium salicylate. A white powder sparingly soluble in water. Action like diuretin. Useful in *arterio-sclerosis* and *asthma*. *Dose.*—8 to 15 grs. or 0.5 to 1 grm.
4. **Rhodan-Calcium-Diuretin.**—In tablets, each contains calcium-diuretin 7½ grs. and pot. sulphocyante 1½ grs. *Dose.*—One tablet twice or thrice daily.

Pharmacology and Therapeutics of Purine Derivatives

These substances are called purine derivatives because they are derived from xanthine, one of the purine bases, by the substitution of methyl radicals (CH_3) in place of hydrogen.

These derivatives act like caffeine and are powerful diuretics without any side-effects on the nervous system as possessed by caffeine. Diuresis is due to dilatation of renal vessels, large number of functioning glomeruli, increased filtration and diminished reabsorption. They however irritate the stomach and produce nausea and vomiting. Attempts have therefore been made to avoid these unpleasant symptoms and also to enhance their action by combining them with calcium, luminal, etc. Theophylline and sodium acetate is more powerful and is more liable to upset the stomach than theobromine and its salt. Theophylline is contained in injectio mersalyli to prevent its decomposition, to reduce local irritation and help absorption, and to increase diuretic action.

These closely allied substances differ in their therapeutic action. Caffeine stimulates the heart and has only a slight direct action on the kidneys. Theobromine acts much more powerfully on the renal epithelium, and stimulates the heart and lowers blood pressure, dilates coronary

vessels and relieves vascular spasms. Aminophylline dilates the coronary vessels and increases both the contraction and output of the heart It is therefore used in **angina pectoris, coronary occlusion, cardiac** and **renal dropsy** and **cardiac asthma.** Since it stimulates the respiratory centre, it is used in all conditions of respiratory depression with Cheyne-Stokes breathing and in **pulmonary oedema.** In urgent cases, *e.g.* in dyspnoea of heart failure it may be used intravenously in doses of 4 gr. in 10 mils of sterile water or glucose. It is of special value in bronchial asthma, specially in patients refractory to adrenaline, but it must be used either intravenously or intramuscularly as when given by the mouth it is ineffective in severe attacks, though may be used in mild and chronic cases.

Theophylline is a less powerful cardiac stimulant than caffeine but is a more active diuretic than either of the other two. The best results are obtained in chronic interstitial nephritis where there is always sufficient healthy kidney tissue left to respond to the drug. It is *contra-indicated in acute nephritis and in diffuse parenchymatous inflammation.* All these diuretics, but specially theophylline, increase the solid constituents as well as the water. This places theophylline amongst the most efficient of diuretics in cases of oedema with retention of sodium chloride.

Theobormine is usually given either as the double salt with sodium salicylate (*diuretin*), or with sodium acetate (*agurin*). Agurin is free from most of the unpleasant side-effects of diuretin especially the depressing action of the salicylate, while the diuretic action is somewhat increased, since the acetate itself possesses diuretic properties and the amount of theobromine contained in agurin is 10 p.c. more than in diuretin. It is most successful in cases of dropsy due to myocardial degeneration, complicated with nephritis and even in uncomplicated cases.

Theophylline may either be given alone, or in the form of theophylline sodium acetate. It is very prompt in its action but the effects soon pass off and it cannot be administered continuously for any length of time.

UREA

Urea. $CO(NH_2)_2$

Syn.—Carbamide.

Source.—Urea may be prepared from ammonium cyanate. It is diamide of carbonic acid.

Characters.—Colourless, transparent, prismatic crystals ; no odour ; taste, saline cooling. *Soluble* in 1 part of water, in 5 parts of alcohol (90 p.c.), insoluble in solvent ether and in chloroform.

B. P. Dose.—75 to 225 grs. or 5 to 15 grms.

NON-OFFICIAL PREPARATION

1. **Quininae et Ureae Hydrochloridum**, B.P.C. *Syn.—Urea Quinine.* Contains [illegible] p.c. quinine. In colourless, translucent prisms. Soluble in water. Used

hypodermically in *malaria* and for local *anaesthesia*. **Dose.**—Subcutaneous or intra-muscular ; 1/2 to 15 grs. or 0.03 to 1 grm.

Pharmacology and Therapeutics

Urea is rapidly absorbed from the intestine and acts as a powerful **diuretic** by preventing normal reabsorption of water by maintaining the osmotic tension of urine. Since it is rapidly excreted its effects are of very short duration. It is used in the treatment of dropsy. Miller and Feldman* treated cardiac dropsy with massive doses of urea (10 to 25 grms.) thrice daily in 40 p.c. solution with very good results. Some fruit juice is added to cover the taste. When about 50 grms. were given daily most of the oedema disappeared. Some cases regained their cardiac efficiency without the use of digitalis.

It is not utilised in the body, and when given in larger doses it is entirely eliminated by the kidneys. Since its elimination is impaired in chronic interstitial nephritis and not in chronic parenchymatous nephritis, it is used as a diuretic in the latter condition. In combination with quinine (urea quinine) it is used in 0.5 to 1 p.c. solution by injection as a local anaesthetic, as a substitute for cocaine. It is non-toxic, and the effect may persist from four hours to several days. A 5 p.c. solution has been injected between the vein and the mucous membrane of the rectum in *internal piles*.

Urea is largely used for testing the efficiency of the kidneys, for which purpose 15 grms. (225 grs.) dissolved in 100 mils ($3\frac{1}{2}$ oz.) of distilled water, are given by the mouth on an empty stomach after emptying the bladder, and its excretion determined at suitable intervals. Figures below 1.5 p.c. collected one hour after and 2 p.c. after two hours show a poor concentrating power of the kidneys and indicates renal inefficiency. Normal kidneys may concentrate up to 4 p.c. or over.

Locally urea is used as a dressing for infected wounds and is specially useful when combined with sulphanilamide when it increases the activity of the latter and makes resistant strains of bacteria more susceptible to sulphanilamide. Used as an ointment (10 p.c. of each) in a hydrophilic base.

SPIRITUS AETHERIS NITROSI. (Sp. Aether. Nitros.). **Syn.**—Sweet Spirit of Nitre.

Source.—Spirit of Nitrous Ether is a mixture of alcohol (90 p.c.), nitric and sulphuric acids, and copper ; containing 1.25 to 2.5 p.c. w/v of ethyl nitrite.

Characters.—A transparent faintly yellow, liquid ; odour penetrating apple-like ; taste, characteristic. It should be kept in small closed container, protected from light, and stored in a cool place.

**British Medical Journal, Jan.* 21, 1933.

Incompatibles.—Potassium and other soluble iodides, iron sulphate, antipyrin, salicylates, tannic and gallic acids, and emulsions.
B. P. Dose.—15 to 60 ms. or 1 to 4 mils.

PHARMACOLOGY AND THERAPEUTICS

Internally.—Spirit of nitrous ether possesses the combined properties of ether and nitrites which it contains, but in a milder degree. It is therefore a mild diffusible stimulant, antispasmodic and carminative.

Circulation.—It accelerates the cardiac activity and relaxes the peripheral blood-vessels, but not to such an extent as the nitrites. By dilating the renal and cutaneous vessels, it acts as a diuretic and diaphoretic respectively and acts as an **antipyretic.** It forms one of the chief ingredients of a fever mixture and is specially valuable in **fevers** during dentition of infants. As a **diuretic** it is used in Bright's disease after the acute inflammatory stage is passed. Dropsies of renal origin are reduced by its use, but it does little good in those of the cardiac type. One of the draw-backs to its use in children is that sometimes it **has a nauseating effect.**

Elimination.—It is excreted by the kidneys and the **lungs.**

VEGETABLE DIURETICS

Juniper, Scoparium, Buchu (*see* page 421), **Punarnava** (*q.v.*).

OLEUM JUNIPERI, I.P.L.—The oil distilled from the ripe berries of *Juniperus macropoda*, and rectified. Colourless or pale greenish-yellow; odour, characteristic; taste, warm aromatic bitter. *Solubility.*—1 in 4 of alcohol (95 p.c.).
Contains (1) *Pinene* ($C_{10}H_{16}$), *Camphene* ($C_{10}H_{16}$), Terpinenol and Cadinene ($C_{15}H_{24}$) (2) Juniper camphor, a crystalline body.
Dose.—1/2 to 3 ms. or 0.03 to 0.2 mil.

NON-OFFICIAL PREPARATION

1. **Spiritus Juniperi.**—1 in 10. *Dose.*—5 to 20 ms. or 0.3 to 1.2 mils.

ACTION AND USES.—Oil of juniper resembles oil of turpentine in its action, but it is a more powerful **renal stimulant** and **diuretic**, and is more agreeable to the stomach. In large doses it causes strangury and priapism. It is absorbed into the blood and is excreted with the urine, to which it imparts an odour of violets.

It is chiefly employed as a diuretic in cardiac and hepatic dropsy, and in chronic nephritis. It should not be used in acute renal affections. It is best given with salines.

SCOPARIUM. B.P.C. Syn. *Broom Tops.*—The fresh and the dried tops of *Cytisus scoparius*. Contains (1) *Scoparin*, a yellow crystalline substance. (2) *Sparteine*, a liquid volatile alkaloid. (3) *Genisteine*, a crystalline volatile alkaloid. (4) ***Sarothamnine*, a non-volatile alkaloid.**

NON-OFFICIAL PREPARATION

1. **Infusum Scoparii Recens. B. P. C.**—Made with *dried tops*. 1 in 10. *Dose.*—1 to 2 ozs. or 30 to 60 mils.

ACTION AND USES.—Broom, because of scoparin, acts as a valuable **diuretic**. It is usually prescribed with other diuretics in all forms of **dropsy** especially cardiac, and interstitial nephritis. Haustus Scoparii Compositus, consisting of Potassium Tartrate 20 grs., Sp. Juniperi 30 ms. and Infusum Scoparii Rec. ad. 1 oz., is a very valuable combination, but it should not be prescribed in acute Bright's disease.

For action of Sparteine, see page 263.

Saline Diuretics

Since all substances eliminated by the kidneys mus remain in solution the amount of urine will depend upo the solid contents to be excreted by the urine. The solid that are eliminated by the kidneys are the "low threshold" substances. They are potassium, sodium, ammonium chlorides, acetates, citrates, nitrates and to a less exten phosphates and tartrates, together with urea and creati-nine. These salts are rapidly absorbed and pass into th plasma increasing its osmotic tension, and since the norma equilibrium has to be maintained, the blood in its tur draws fluid from the tissues making it hydraemic. It fol-lows therefore that any increase in the intake of any o these substances will result in increased diuresis. Being "no threshold" substances they are not reabsorbed fro the tubules when they reach the kidney, hence the urinar water is increased and possibly also the glomerular pres-sure, resulting in an increase of non-colloidal constituen of the blood and increased glomerular filtration. There-fore the best oral saline diuretic is one with both ions o low threshold value.

The Saline Diuretics are :—

Chloride of Ammonium and **Calcium**, and **Nitrate of Ammonium** (these caus acidosis) ; **Acetate** and **Citrate of Sodium** and **Potassium** ; **Acetate** and **Citrate** o **Ammonium** which are eliminated as urea ; **Acid Potassium Tartrate** and **Nitrat of Potassium.**

Class B : **Urinary Antiseptics**

Infection of the urinary tract may be acute accom-panied by fever or may be chronic. The common caus of infection is by *Bact. coli* which may be a part of genera infection from the blood stream or infection may b carried to the blood by external agencies, *e.g.* catheterisa-tion. Infection of the urethra and bladder may be treate by irrigation with antiseptics, like the silver preparations potassium permanganate, acriflavine, etc. The infectio of the upper part of the urinary tract or of the bladder i best treated with drugs that are eliminated with the urine

In order that a drug may act as a genito-urinary anti-septic it must be absorbed through the alimentary cana and excreted by the kidneys. Many antiseptics are how-ever eliminated in an inactive form and are therefore use-less as genito-urinary antiseptics. But the drugs of thi group are of special value in disinfecting the genito-urinar tract during their elimination in more or less concentrate form. The continual excretion of these drugs throug this channel reduces the number of organisms in the urin and prevents sepsis.

Reaction of the urine has an important bearing on th growth of bacteria most of which grow freely in a neutra or feebly alkaline urine. Their growth is inhibited in a

ine with pH 5. As a rule however *Bact. coli* flourish in a acid urine and are inhibited if the urine is rendered lkaline, and this is followed by improvement of the ymptoms. It should be noted that *Bact. coli* grows freely n urine over a range of pH 5.5 to 8.5. Therefore most of he bacteria can be killed if the urine is rendered highly cid or highly alkaline. Unfortunately it is not possible o maintain the acidity of the urine below pH 5.3 for a rolonged period without producing renal irritation.

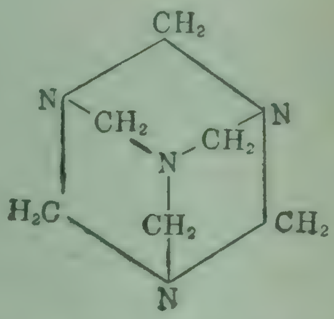
The action of genito-urinary antiseptics largely de-ends upon the reaction of the urine which considerably nfluences the growth of bacteria in the urine. Thus it has een shown that although normal urine undergoes putre-faction in about 36 hours, it takes only 24 hours if rendered lkaline by the administration of alkaline salts. On the ther hand it takes three days to putrefy if it is rendered cid by the administration of acid sodium phosphate.

The commonly used urinary antiseptics are :—

1. **Ammonia Formaldehyde Group**
   Hexamine.
2. **Various acids and their salts**
   Mandelic Acid, Benzoic acid and Benzoates, Salicylic Acid and Salicylates and Boric Acid
3. **Coal-tar Dyes**
   Mercurochrome, Acriflavine, Methylene Blue, Pyridium
4. **Sulphonamide Group**
   Sulphadiazine, Sulphathiazole, etc. (*q.v.*)
5. Antibiotics
   Penicillin, Streptomycin, Aureomycin
6. Certain Essential Oils
   Sandal Wood Oil, Buchu, Cubebs (*q.v.*)

HEXAMINA, B.P.C. Syn.—Methenamine; "Urotropine"; Amino-rm ; Formin.

Source.—Hexamine is obtained y the combination of ammonia and rmaldehyde. Contains not less han 99 p.c. of pure hexamethylene-tramine.



Characters.—Colourless crystals or a hite crystalline powder. Inodorous. Taste, t first sweetish, afterwards bitter. *Solubility*.—1 in [illegible] of water and 1 in 8 of alcohol p.c.r. Solution alkaline to litmus. *Dose.*—10 to 30 gr. or 0.6 to 2 grm.

NON-OFFICIAL PREPARATIONS

1. **Piperazina.**—Formed by the action of [illegible] on ethylene dibromide. In small [illegible] deliquescent crystals, with a strongly [illegible] reaction, [illegible] taste and faint odour. Soluble in water. In uric acid dia-thesis, gout and lithiasis. *Dose.*—5 to 15 grs. or 0.3 to 1 grm.

2. **Hexamine Glycocholate.** *Syn.*—*Felamine.*—Cholagogue and biliary anti-septic.—In *catarrhal jaundice*, after-treatment of typhoid fever and in gall-stones [illegible] grs. or 0.3 grm. in tablets.

3. **Helmitol.** *Syn.*—*Formamol* ; *New Urotropine.*—A citrate combination of [illegible] and formaldehyde. A more powerful antiseptic than hexamine and [illegible] causes irritation of the urinary apparatus. *Dose.*—8 to 15 grs. or 0.5 to 1 grm.

4. **Pyridium.** *Syn.*—*Mallophen.*—Phenyl-azo-alpha-diamino-pyridine hydrochloride. [illegible] crystalline powder, slowly soluble in cold water, glycerin, alcohol. [illegible] A powerful bactericide in gonococcal and staphylococcal infections of the genito-urinary tract. Useful in gonorrhoeal infection and complications of males and females, [illegible] and cystitis. *Dose.*—Each tablet contains $1\frac{1}{2}$ grs. or 0.1 grm. [illegible] at a time after meals.

Pharmacology and Therapeutics

Hexamine is rapidly absorbed and appears in the urine with an hour after administration. The quantity appearing in the uri varies with its absorption, about 20 to 30 p.c. being decomposed the stomach during digestion, but only about 1 p.c. during fast when the contents are feebly acid.

It is a powerful **urinary antiseptic**, but by itself it has no an septic power, and its value depends upon the formation of form dehyde in the acid urine which should be below pH 5.6. It has be recommended in typhoid fever not only to lessen the chance of cy titis but also to prevent the spread of infection. It is largely us in *Bact. coli* infection of the urinary tract. In this condition t urine is already highly acid and the use of hexamine alone w render the urine sterile. But a highly acid urine irritates the u nary tract, therefore it is often desirable to use large doses alkalies (citrates or acetates) to make the urine alkaline, and sin the growth of colon bacillus is inhibited in an alkaline urine th will not only relieve irritation but will also prevent further grow of the organisms. If the infection of the urinary tract is due pyogenic cocci or putrefactive organisms the urine becomes foul a alkaline, as in cases of cystitis and pyelitis and it requires to be re dered acid for hexamine to act. To ensure acidity of the ur acid sodium phosphate should be given in doses of 20 to 30 grs.; sodium benzoate in doses of 5 to 30 grs.; or ammonium chloride to 20 grs., three times daily. The dose should be adjusted to ma the urine acid to litmus. In generalised infection with *coli* or anisms hexamine given intravenously (2 to 5 mils of 20 to 40 p. solution) gives good results.

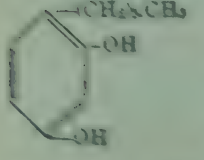
It has been used in infection of the gall-bladder, pyelitis pregnancy and post-operative anuria. Although it is said that formaldehyde is formed in the bile because of its feeble alkal reaction, Hurst has pointed out that it can produce a disinfecta action when given in large doses (60 to 100 grs. daily). Large dos of alkalies are necessary to keep the urine alkaline to prevent ren irritation.

It has been found in the bile, cerebro-spinal fluid and pancreat juice and has therefore been used in cerebro-spinal meningiti poliomyelitis of children and various inflammatory diseases of t meninges and brain, although there is little evidence that hexami is converted into formaldehyde in the cerebro-spinal fluid.

It begins to be excreted within 10 to 15 minutes and continu for several hours. It should therefore be administered frequent i.e. **at least four times a day.**

When given in 10 gr. doses it produces so little formaldehy that the concentration cannot reach the zone at which bacteric action occurs. On the other hand higher doses are irritating. hexamine is limited in its usefulness. Nevertheless continued pr sence of quite low concentration of formaldehyde in the urine h some effect in inhibiting the growth of organism in cases of chro infections.

Hexylresorcinol. B.P.C. Syn.—Caprokol.—Hexylresorcinol



4-n-hexylresorcinol. The introduction of an alk radical to resorcin markedly decreases the toxic and at the same time increases its germicidal act vity. It is a valuable **urinary disinfectant and** do **not irritate the urinary tract, and the** germ cidal action is not modified by the natural range the reaction of the urine, but it is destroyed by t use of large doses of bicarbonate of soda. It a mainly by lowering the surface tension of the urine and thus rend

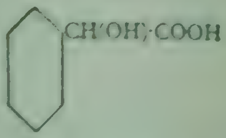
diffuses into the renal tissues and bacteria. During this treatment the fluid intake should be restricted. It is more potent in *coccal* infection than in *coli-form* bacillary infections. It is administered in capsules (0.15 grm. in olive oil or as 2½ p.c. solution in olive oil) 2 to 4 capsules three daily immediately after food or 3 to 6 drs. of the solution; each dr. contains 0.1 grm. (1½ grs.). Valuable in cystitis and pyelitis due to *staphylococcus and Ps. pyocyanea*. Produces local necrosis when given hypodermically. For its anthelmintic action, *see* page 397.

Dose. 2 to 15 gr. or 0.12 to 1 grm.

ACIDUM MANDELICUM

(Acid. Mandelic.)

Syn.—Phenylglycollic Acid.



Source.—Mandelic Acid is prepared by the action of sodium cyanide on the addition compound of benzaldehyde with sodium bisulphite, and hydrolysis of mandelonitrile thus produced.

Characters.—In white crystals, slowly turning yellow when exposed to light. Almost odourless; taste, acid and saline. *Soluble* in about 7 parts of water and in about 1 part of alcohol (95 p.c.).

B. P. Dose.—30 to 60 grs. or 2 to 4 grms.

Calcii Mandelas. (Calc. Mandel.). $C_{16}H_{14}O_6Ca$.—Calcium Mandelate is a white micro-crystalline powder; odour, slightly aromatic; taste, slightly saline. Very slightly *soluble* in water; insoluble in alcohol (90 p.c.).

B. P. Dose.—30 to 60 grs. or 2 to 4 grms.

Non-official Preparations

1. **Sodii Mandelas.** In white crystals with faintly aromatic smell. Soluble in about 1½ parts of water. *Dose.*—60 grs. or 3.4 grms.
2. **Ammonii Mandelas.**—In white hygroscopic needles, very easily soluble in water and alcohol. *Dose.*—60 grs. or 3.4 grms.

Action and Uses

It has been pointed out that the reaction of the urine has considerable influence not only on the efficiency of urinary antiseptics but also on the bacterial population and naturally many of the methods of treating urinary infections have necessitated some control over the reaction of the urine. While alkalies and alkaline salts judiciously administered will produce satisfactory degree of alkalinity, but to render urine acid and to maintain it at a definite pH level is not so easily attained. Apart from drugs, diet also markedly influences the reaction of the urine, and can, if suitably arranged, multiply or reinforce the action of drugs. By giving ketogenic diet the urine can be made sufficiently acid. In fact Clark (1931) by giving patients a diet containing a large quantity of fat and a minimum of carbohydrate caused incomplete combustion of fat with the result that β-hydroxybutyric acid appeared in the urine, which not only rendered urine acid but acted as a powerful bactericidal agent. Since β-hydroxybutyric acid cannot be given by the mouth as it is destroyed in the upper part of the alimentary canal, and treatment of patients by

ketogenic diet is unreliable and difficult to control, mandelic acid has been found to be an effective substitute. With an acidity below pH 5.5 it is a powerful bacteriostatic or bactericidal, and is specially valuable in *Bact. coli* pyuria, cystitis and in pyelitis of pregnancy and puerperium. It is also valuable in infection of the urinary tract with *Str. faecalis*, and possibly in other infections, *e.g. Staphylococcus albus.*

Instead of the acid, which is more irritating, sodium or ammonium mandelate is generally used. The method is to administer sodium mandelate to be preceded by another mixture containing ammonium chloride.* But ammonium chloride often causes nausea and vomiting. To avoid this ammonium mandelate was introduced. Since ammonia is converted into urea, the liberated mandelic acid acidifies the urine. Calcium mandelate has superseded the ammonium salt and is used in doses of 4 grms. (60 grs.) four times a day. It is pleasanter to take and less irritant.

To be successful the urine must be strongly acid and the pH value should be 5.5 or less. With a moderate restriction of fluid this degree of acidity is easily obtained but if it does not then ammonium chloride should be given in 15 gr. doses 4 times a day, or if necessary 5 to 6 times a day, but should not be continued for more than 2 to 3 days in this high dose.

Many proprietary preparations are now on the market which are easy of administration and do not require separate use of other drugs to make the urine acid. These are used in doses of two teaspoonfuls in 2 ozs. of water four times a day, after meals. The treatment should be continued for ten days and during this period the fluid intake should be limited to two pints daily in order to ensure a high concentration of mandelic acid in the urine.

Contra-indications.—It occasionally causes diarrhoea, haematuria, dysuria, and should not be given when there is impairment of renal function.

OLEUM SANTALI. (Ol. Santal.). **B.P.C. Syn.**—*Chandane Tel*, Beng.—Oil of Sandal Wood is the oil distilled from the dried heartwood of *Santalum album.*

Characters.—Pale yellow or nearly colourless, viscid liquid ; odour, strongly aromatic ; taste, unpleasant.

Composition.—The chief constituent is (1) *Santalol*, a mixture of two sesquiterpene alcohols. (2) An aldehyde, *santalal.* (3) Esters, free acids, etc.

Dose.—5 to 15 ms. or 0.3 to 1 mil.

* No. 1 Ammonium Chloride Mixture.

Ammon. chlorid.	oz.	1
Ext. glycyrrh. liq.	ms.	240
Aqua	ad. oz.	8

One table-spoonful in water 4 times a day, before food.

No. 2. Sodium Mandelate Mixture.

Sodium mandelate	oz.	1½
Syr. aurant.	oz.	1½
Aqua	ad. oz.	8

One table-spoonful in water 4 times a day after food.

Uses

Oil of sandal wood is eliminated by the genito-urinary tract which it stimulates and disinfects. It is used in 15 to 20 ms. doses three times a day in **acute and chronic gonorrhoea.** It must be continued for two weeks to prevent a recurrence. It is an antiparasitic and **may be used in scabies.**

BUCHU, B.P.C. **Syn.**—Buchu Folia; Bucco; Diosma.—The dried leaves of *Barosma betulina.*

Composition.—(1) A *volatile oil* (1.3 to 2 p.c.), containing *diosphenol*, which forms crystalline deposits on exposure. (2) *d*-limonene, dipentene and menthone, mucilage and diosmin.

Non-official Preparations

1. **Infusum Buchu Concentratum, B.P.C.**—40 p.c. *Dose.*—60 to 120 ms. or 4 to 8 mils.
2. **Infusum Buchu Recens, B.P.C.**—5 p.c. *Dose.*—1 to 2 ozs. or 30 to 60 mils.
3. **Tinctura Buchu, B.P.C.**—1 in 5. *Dose.*—30 to 60 ms. or 2 to 4 mils.

Action and Uses.—The action of buchu is due to the volatile oil which it contains, and it is a **diuretic** and **mild urinary antiseptic.** The volatile oil is readily absorbed and is mostly excreted by the kidneys which it stimulates. During its elimination it soothes and disinfects the urinary passages and imparts a peculiar odour to the urine. It is chiefly used to allay the irritability of the urinary tract, especially the bladder, and is therefore very serviceable in cystitis, irritability of the bladder, urethritis, gonorrhoea, pyelitis, etc. If continued too long in large doses it may harm the kidneys. It is largely used as fresh infusion which forms a good vehicle for mixtures.

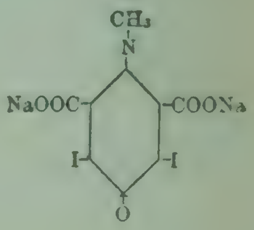
Class C : **Drugs used for diagnostic purposes**

1. **For X'ray Examination ; Iodoxyl, Diodone.**
2. For investigation of renal efficiency ; **Urea** (*see* page 413), **Methylene Blue** (*q. v.*), **Indigo Carmine, Phenol-Red.**

IODOXYLUM
(Iodoxyl.)

Syn.—Uroselectan-B ; Uropac ; Pyelectan.

Source.—Iodoxyl is the disodium salt of N-methyl-3 : 5-diiodo-4-pyridone-2 : 6-dicarboxylic acid. It contains from 50.5 to 52.5 per cent. of I, and from 9.2 to 9.4 per cent. of Na.



Characters.—A white powder ; odourless. *Soluble* in 1.2 parts of water, and in 100 parts of alcohol (90 p. c.) ; **insoluble in solvent ether and in chloroform.**

B. P. Dose.—By intravenous injection, 150 to 225 grs. or 10 to 15 grms.

Action and Uses

Iodoxyl forms a readily soluble and stable solution with water and since no iodine is liberated in the body it rarely produces any toxic symptoms except in susceptible persons. Minor reactions may occur, they are thirst, a feeling of heat over the body, flushing of the face, and rarely pallor, sweating, and prostration.

It is used *intravenously* to take X-ray photographs of the urinary tract. The dose for adult is 20 mils (5 drs.) of a 75 p.c. solution ; and for children the dose is 1 mil (15 ms.) for every year with a minimum of 3 mils (45 ms.).

The injections are made very slowly at least 5 minut[...] being taken for the operation, and since the solution [...] strongly hypertonic care should be taken that no fluid leak[...] into the surrounding tissue. The photographs are taken [...] to 20 minutes after the injection at the time of maxim[...] excretion. As long as the kidneys are healthy and func[...]tioning normally the results are satisfactory, but danger[...]ous in acute nephritis. If the kidneys are not functionin[...] properly its excretion may be delayed and pyelograph[...] cannot be taken till sufficient is excreted, which may tak[...] several hours. The rate of excretion gives some idea o[...] the extent of renal function. In bad cases the drug is no[...] excreted and no pyelograph can be taken.

Contra-indications.—Severe disease of the liver, uraemia.

INJECTIO DIODONI. **Syn.**—Liquor Diodoni; Solution o[...] Diodone; Perabrodil.—Injection of Diodone is a sterile aqueous solu[...]tion of 3 : 5-diiodo-4-pyridone-N-acetic acid. A clear almost colour[...]less liquid.

B. P. Dose.—*By intravenous injection*:—For an adult, 300 ms. (20 ml.). F[...] a child, 120 to 150 ms. (8 to 10 ml.). For an infant, 30 to 45 ms. (2 to 3 ml.).

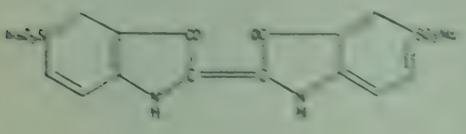
Action and Uses.—Injectio Diodoni is used as a contras[...] medium to take X-ray photographs in the same way as iodoxyl. [...] is however less irritant to the tissues and does not depress the hear[...] If the kidneys are healthy radiographs may be taken in from eig[...] to twenty minutes. In cases where a suitable vein cannot be foun[...] it may be given subcutaneously, but its excretion is delayed an[...] therefore photographs should be taken after 30 minutes to one hou[...]

Contraindications.—Nephritis, tuberculosis, hepatic disease, a[...] in idiosyncrasy to iodine.

INDICARMINUM. (Idicarmin.). $C_{16}H_8O_8N_2S_2Na_2$.

Syn.—Sodium Indigotindisulphonate.

Source.—Indigo Carmine is prepared by the action of sulphur[...] acid on indigotin, neutralising it with sodium carbonate, and pr[...]cipitating with sodium chloride.



Characters.—A blue powder, or bl[...] granules with a coppery lustre. [...] odour; taste, saline. Soluble in [...] parts of water, readily soluble [...] warm water. Precipitated by sodi[...] chloride.

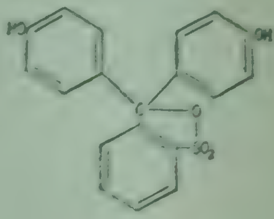
B. P. Dose.—3/4 to 1½ grs. or 0.[...] to 0.1 grm. (subcutaneous or intra[...]muscular injection); 1/8 to 1/4 [...] or 8 to 16 mg. (intravenous.).

Uses

Indigo carmine is used either intravenously or by intramuscul[...] injection to test the renal function and for diagnosis of surgic[...] affections of the kidney. Four to ten mils (60 to 150 ms.) of a [...] p.c. solution is usually given intramuscularly into the glute[...] muscle. The colour should appear within 7 to 10 minutes, and th[...] depth of the colouration gives a clue to the renal efficiency. It ha[...] also been used for the investigation of liver function. After intr[...]muscular injection it is excreted by the healthy subject after [...] minutes and reaches maximum concentration within 2 to 3 hour[...] When the liver is diseased it is excreted earlier or later accordi[...] to the nature of the affection of the organ. In diabetes it is earli[...] in venous cirrhosis it takes a longer time. In pernicious anaem[...]

is delayed and the total quantity is less than usual. In cases of jaundice there is no excretion at all in the bile.

PHENOLSULPHONPHTHALEINUM. Syn.—Phenol Red. A bright to dark red crystalline powder; odourless. *Soluble* in about 1300 parts of water and in about 350 parts of alcohol (95 p.c.), *readily soluble* in solutions of alkali hydroxides and of alkali carbonates.



B. P. Dose.—1/10 gr. or 6 mg. by *intramuscular or intravenous injection.*

Uses.—Phenolsulphonphthalein is used to test the renal function. After an intravenous injection of 60 mg. (1 gr.) in 1 mil (15 m.) not less than 50 p.c. for the first hour, or 75 p.c. for the first and second hours should be excreted in the urine. It is used as an indicator to determine hydrogen-ion concentration of urine.

GROUP XV

DRUGS ACTING ON THE GENITAL ORGANS

Uterus.—The action of drugs on the uterus is difficult to analyse. Experiments made with isolated organs or on intact animals show that the movements are irregular and differ in different animals. The virgin, the pregnant and the non-pregnant uteri also show different types of activity. The movements are myogenic and although not affected by the section of the uterine nerves yet the activity is regulated by the extrinsic nerves. A characteristic feature of the uterine muscle is that it is subject to cyclical changes which occur during menstruation and more specially during pregnancy.

The uterus is supplied by the sympathetic through the hypogastric which contains both the excitor and inhibitor nerves. Stimulation of the sympathetic therefore is followed by a mixed effect, and the contraction or relaxation depends upon the relative preponderance of the two sets of fibres, but this varies in different species of animals and even in the same species, whether virgin or pregnant. The sympathetic contains both adrenergic and cholinergic fibres. Thus physostigmine and acetylcholine increase uterine contraction. The parasympathetic supply is rather feeble and uncertain and is not generally recognised.

The study of the uterine movements can be made either in the intact animal or in the isolated organ. The movements of the human uterus can be observed with X-rays after filling the cavity with lipiodol; or by using in a bath strips of healthy uterus after an operation and recording its movements.

The pregnant uterus is more sensitive to the effect of drugs than the virgin or non-pregnant one. During pregnancy the uterus undergoes spontaneous contraction which becomes stronger towards the latter part of pregnancy.

The pharmacology of the uterus is however more complicated owing to the fact that apart from the nervous influences the function is controlled and regulated by a complicated arrangement of the different endocrine glands. Further, this hormonic control is extremely complex and is further complicated by the wide variation in the sexual functions in different species of animals. The cyclic changes in the ovary are regulated by the anterior pituitary.

The phenomena of menstruation depend upon the state of the endometrium, activity of the ovaries, and the normal secretion of the anterior pituitary gonadotrophic hormones. These hormones

(follicular stimulating and luteinizing) are responsible for the onset of ovarian activity at puberty, for the regulation of follicular ripening and corpus luteum formation. Removal of the ovaries is followed by stoppage of menstruation (artificial menopause) with atrophy of the uterus. In congenital absence of the ovaries, or when they are undeveloped, a condition similar to amenorrhoea follows. The luteal hormone, *progesterone*, is of great value for the maintenance of pregnancy, and implantation of ovum cannot occur in the absence of the corpus luteum which enlarges during pregnancy, and its hormone has an inhibitory effect on uterine contraction while its removal in early pregnancy is followed by abortion. Abortion in the early months of pregnancy has been ascribed to excessive production of oestrogen in relation to that of progesterone. Towards the end of pregnancy the corpus luteum degenerates and the uterus becomes hypersensitive and reacts to an increased secretion of oxytocin from the posterior pituitary resulting in termination of pregnancy.

Ecbolics or oxytocics are drugs which cause expulsion of the contents of the uterus by contracting the uterine muscle. They may be *direct* or *indirect*.

Direct ecbolics act by stimulating the uterus to contraction. They are, histamine, posterior pituitary, quinine, barium and lead, these act by stimulating the muscle directly ; tyramine, ergotoxine and ergometrine, by stimulating the motor sympathetic endings ; and strychnine which stimulates the centre. Hydrastis probably acts in the same way as ergot or pituitary. Of these, pituitary extract, ergot and histamine are most powerful and reliable. Lead is often used as an abortifacient for criminal purposes.

Indirect ecbolics act by producing congestion of the pelvic viscera. They are drastic purgatives and aloes ; irritating oils like savine and pennyroyal ; irritants like cantharidin, etc.

Emmenagogues are drugs which increase or restore menstrual flow when deficient or absent. They cause congestion of the pelvic viscera. Most ecbolics when used in small doses to non-pregnant women act as emmenagogues. Oestrin, the active hormone found in the ovaries and in the urine during pregnancy is chemically related to cholesterol, when injected produces oestrus in rats. It has been found to give relief in cases of artificial menopause and in regulating menstrual disorders. Heat or counter-irritants applied over pelvic regions, *e.g.* hot hip bath, hot mustard poultice help the onset of menstruation. Amenorrhoea is common in women suffering from anaemia, chronic malaria, cachexia and in general rundown conditions, when appropriate treatment with iron, codliver oil or other tonics are helpful. Aloe is useful when due to constipation.

Mammary Glands.—These glands are intimately related to the sex glands, and their development is arrested after extirpation of the ovaries, while their growth continues in the normal way after successful transplantation in young animals. Moreover, lactosecretory hormone (prolactin, galactin) secreted by the anterior pituitary is essential to initiate and maintain secretion of milk and for the growth of the gland during pregnancy. In fact injection of anterior pituitary causes hypertrophy of the mammary tissue and secretion of milk in ovariectomised virgin rabbits. Just as the development of the glands is regulated by the internal secretion of the ovaries, corpus luteum and the placenta, so also the secretion of milk is regulated by hormones.

Galactogogues are drugs which increase the secretion of milk. An injection of placental extract increases the secretion of milk ; so does pituitary extract. The secretion of milk is also influenced by various other factors and reflexes. It is possible that the nerve supply of the mammary glands is different from other glands. Thus

pilocarpine, which increases the secretion of other glands, has no effect on the secretion of milk. Prolactin preparations have been used to increase secretion of milk. Urea is supposed to be a true galactogogue.

Antigalactogogues are drugs which diminish the secretion of milk; as iodides and oestrin which act by inhibiting secretion of prolactin.

Several drugs are excreted by the milk and in doing so alter its composition. Thus rhubarb, senna, jalap, scammony and castor oil may produce looseness in suckling babies when given to their mothers. Iodides, bromides, sulphonamides, arsenic and mercury have been found in the milk when given to women. Asafetida and oil of turpentine impart a disagreeable odour to the milk. Opium given to nursing mothers may cause symptoms of poisoning to infants.

Placenta.—Human placenta contains (a) oestrone or theelin, oestrol or trihydroxyoestrin or theelol; and (b) anterior pituitary-like (A.P.L.) substance or chorionic gonadotrophin. This has action similar to but not identical with the gonadotrophic principle of the anterior pituitary. The gonadotrophin of the placenta serves to supplement the action of the pituitary in maintaining the growth of the corpus luteum during pregnancy. Placenta therefore furnishes a hormone which acting through the mediation of the ovary (corpus luteum) ensures its own physiological integrity.

Aphrodisiacs.—These are drugs which cause sexual excitement and increase sexual power. The centre lies in the lower part of the spinal cord, and excitement can be produced purely reflexly by sensory stimuli from various parts such as the nose, eye, ear, mamma, etc. It is probable that the centre for erection is affected reflexly by the fullness of the bladder and of the seminal vesicles. The centres are also controlled by internal secretions. Steinach has shown that the embracing reflex which disappears after castration, reappears after injection of testicular substance. This he attributes to the internal secretion of the interstitial tissue and, not to that producing spermatozoa. The internal secretions of thyroid and of the hypophysis play important part in the development of the genital organs. Aphrodisiacs are :—Strychnine, damiana, yohimbine, etc.

Anaphrodisiacs are drugs which diminish sexual passion and power. These are iodides, bromides, belladonna, etc.

Class A : Ecbolics

Ergot, Histamine, Hydrastis, Pituitary Extract

ERGOTA

Ergot. (Ergot.)

Syn.—Secale Cornutum ; Ergot of Rye.

Source.—The sclerotium (mycelium or spawn) of *Claviceps purpurea* arising in the ovary of *Secale cereale*, the common rye. Contains not less than 0.2 p.c. of the total alkaloids of ergot, calculated as *ergotoxine* of which not less than 15 p.c. consists of water-soluble alkaloids of ergot, calculated as ergometrine.

Characters.—Dark violet to nearly black ; usually from 1 to 4 cm. long and from 2 to 7 mm. broad, fusiform, obscurely 3 or 4 sided, straight or arcuate ; longitudinally furrowed and transversely cracked ; brittle ; whitish or pinkish-white internally, showing darker lines radiating from the centre. Odour and taste, characteristic.

Composition.—By the growth of the fungus the proteins of the rye are broken down and various amino-acid derivatives are formed, to which ergot owes its properties. The chief constituents are :—

I. **Alkaloids** :—Five pairs of optical isomers.

A. Pharmacologically active (laevo-rotatory) :

(1) Water insoluble : (a) *Ergotoxine*, [illegible]. (b) *Ergotamine*, [illegible], (c) Ergosine, [illegible]. (d) Ergocristine, [illegible].

(2) ***Water soluble***—**(a)** ***Ergometrine***, $C_{19}H_{23}O_2N_3$.

B. Pharmacologically almost inert (*dextro-rotatory*), the corresponding alkaloids are :

(1) *Water insoluble*—(a) Ergotinine, (b) Ergotaminine, (c) Ergosinine, (d) Ergocristinine.

(2) ***Water soluble*—(a) Ergometrinine.**

II. **Amines** :—Produced by decarboxylation of certain amino-acids : *Tyramine* from tyrosine, *Histamine* from histidine, Isoamylamine from leucine, Agmatine from lysine, Guanidobutylamine from arginine, and Cadaverine.

III. **Bases** :—Choline, Acetylcholine, Ergothioneine, Uracil, Guanosine.

IV. Sterols :—Ergosterol, Fungisterol.

V. **Inert extractives.**—*Fixed oil* (10 to 35 p. c.), colouring principle (sclererythrin), inorganic salts, and complex proteinogenous substances.

N. B.—*Ergoclavine* and *Sensibamine* are probably molecular compounds of some of the different alkaloids mentioned. *Ergosterine*, *Ergotocine* and *Ergobasine* are probably identical with Ergometrine.

Ergota Praeparata. (Ergot. Praep.).—Prepared Ergot is ergot powdered and immediately deprived of its fat. Contains in 8 grs. 1/60 gr. of the total alkaloids of ergot, calculated as ergotoxine, and 1/400 gr. of ergometrine.

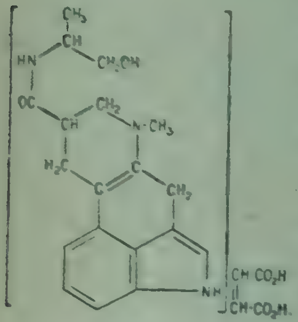
B. P. Dose.—2½ to 8 grs. or 0.15 to 0.5 grm.

Official Preparations

1. **Tabellae Ergotae Praeparatae.—B. P. Dose.—2½ to 8 grs or 0.15 to 0.5 grm.** N. B. When the dose is not mentioned, 2½ gr. tablets shall be supplied.

2. **Extractum Ergotae Liquidum.**—Contains 0.06 p. c. w/v of the total alkaloids of ergot calculated as ergotoxine. After storage contains not less than 0.04 p. c. w/v of ergotoxine, or 1/90 gr. in 20 ms. **B. P. Dose.—10 to 20 ms. or 0.6 to 1.2 mils.**

Ergometrinae Maleas. (Ergometrin. Maleas). **Syn.**—Ergonovine Maleate.—Ergometrine Maleate is the acid maleate of an alkaloid, ergometrine, obtained from ergot.



Characters.—A white, or faintly yellow, microcrystalline powder ; odourless. *Soluble* in about 36 parts of water, in 100 parts of alcohol (90 p. c.), insoluble in solvent ether and in chloroform.

B. P. Dose.—1/120 to 1/60 gr. or **0.5 to 1 mg.** By intramuscular injection :—**1/240 to 1/120 gr.** or **0.25 to 0.5 mg. By intravenous injection :—1/480 to 1/240 gr.** or **0.125 to 0.25 mg.**

Official Preparation

1. **Injectio Ergometrinae Maleatis.** ***Syn.—Ergonovine Maleate Injection.*—B. P. Dose.—**By intramuscular injection :—**1/240 to 1/120 gr. or 0.25 to 0.5 mg.** By intravenous injection.—**1/480 gr. to 1/240 gr.** or **0.125 to 0.25 mg.** N. B. When the dose is not mentioned, **1/120 gr. in 15 ms. shall be supplied.**

Ergotoxinae Aethanosulphonas. (Ergotox. Aethanosulph.). **B.P.C.**—Ergotoxine Ethanesulphonate is the ethanesulphonate of an alkaloid, ergotoxine, obtained from ergot. Contains 83.6 p.c. ergotoxine.

Characters.—Colourless, acicular crystals : odourless. Sparingly *soluble* in **water, more in alcohol (90 p. c.), easily in methyl alcohol.**

Dose.—1/120 to 1/60 gr. or **0.5 to 1 mg.** subcutaneously or intramuscularly.

Non-official Preparations

1. **Basergin.**—A stable preparation of ergometrine tartrate containing 0.25 mg. (1/240 gr.) each tablet, or ampoules of 1 mil contain 0.2 mg. (1/320 gr.). *Dose.*—**1 tablet or 15 ms. or 1 mil. solution for injection.**

2. **Neo-Femergin.** *Syn.—Neo-Gynergen.*—Each tablet contains ergometrine 0.125 mg. (1/480 gr.) and 0.25 mg. (1/240 gr.) of ergotamine.

Ergotoxine.—It has the following effects, *viz.*—(*a*) stimulates and subsequently depresses the sympathetic myoneural junctions, but only when they are motor ; (*b*) stimulates the involuntary muscles directly and renders tissues insensitive to adrenaline. It therefore antagonises the motor effects of adrenaline upon the plain muscles. It increases the tone of almost all the plain muscles throughout the body, but the action on the arteries is most

marked, which become constricted with stasis of peripheral circulation. Subsequently there is thickening of the vessel walls and the small vessels contain hyaline plugs. Small doses injected intravenously stimulate the vessels supplied with vaso-constrictor nerves and cause a rise of blood pressure with slowing of the heart. A second injection causes a smaller rise or no rise at all due to paralysis of the motor nerve-endings of the sympathetic. An injection of adrenaline at this stage causes the arteries to dilate, the so-called "vaso-motor reversal of Dale." As it does not influence the inhibitory sympathetic endings, it has no effect on the contracted bronchioles nor on the stomach or intestinal movements. By stimulating the motor sympathetic endings it increases the tone and rhythmic contraction of the uterus. This action is elicited only on pregnant or parturient uterus. It does not constrict the vessels when locally applied, and since its absorption is not retarded from the stomach like adrenaline all these effects are elicited when given by the mouth.

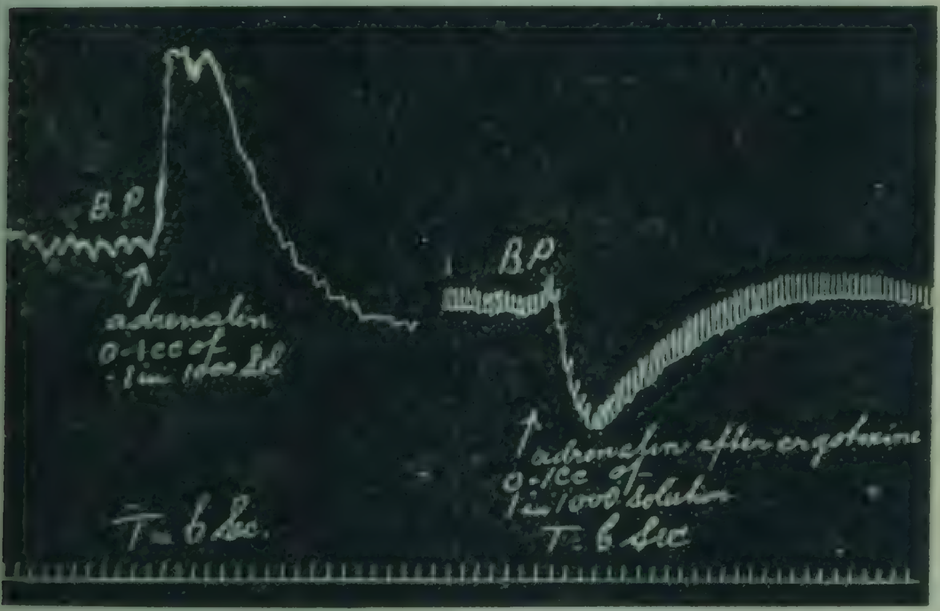


Fig. 27.—Showing phenomenon of Vasomotor Reversal of Dale here the rise of blood pressure with adrenaline and fall of pressure with adrenaline after ergotoxine.

Tyramine.—(1/3 to 3/5 gr.). It acts like adrenaline, but the effects are not so prompt or powerful but are of longer duration. These effects are observed when injected subcutaneously. It contracts the bronchial muscles and therefore does not relieve asthmatic attacks. It causes marked contraction of the uterus specially when pregnant (*see* page 319).

Pharmacology

Inspite of the fact that ergot was used to produce uterine contraction and that various alkaloids have been isolated at different times, the chemistry of ergot was only partially solved. It has been observed that although crude preparations of ergot, like the liquid extract, produced uterine contraction within a few minutes, the administra-

tion of ergotoxine or any other alkaloid required muc longer period to elicit the uterine effect. This was due t the fact that crude ergot contained other active substance which produced the effect, and this was shown by Chassa Moir, who elicited definite effects by the administration o watery extract of ergot, and which did not contain any o the known alkaloids. This was followed by much wor and isolation of a new alkaloid ergometrine, and whic was soluble in water.

Internally. **Gastro-intestinal tract.**—Ergot has a dis agreeable bitter taste and increases salivary secretion Since the sympathetic supply to the intestine is inhibitory ergot has very little effect on the movements of th intestine.

Heart and circulation.—Ergot has decided influence on the heart, which beats more vigorously, the systole i more complete and the output is much greater. Thi effect is due partly to tyramine exciting the sympatheti nerve-endings like adrenaline and partly to ergometrin which stimulates the heart. The rate is slowed from in creased blood pressure stimulating the vagal centre an by the direct action on the muscle.

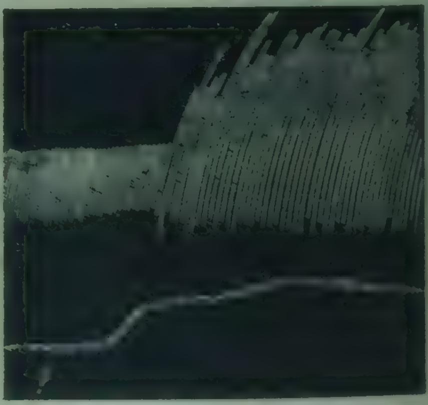


Fig. 28.—Dog. Respiration and Blood Pressure.

At point of arrow 0.5 mil of 1 p. c. solution of ergotoxine was introduced into the femoral vein. Note—stimulation of respiration and rise of blood pressure. After a large dose the respiration is depressed making it slower and weaker.

The effect on blood pressure is variable, no chang being observed unless given intravenously ; this is possibl due to the complex action of its different constituent Given by the mouth there is only a slight rise of pressure When given intravenously there may be a fall of pressur or an initial fall followed by a rise due to the presence i large amounts of histamine or choline. Prolonged con striction of the vessels caused by ergot, if continued long may cause gangrene in different parts of the body. Toxi doses paralyse the vaso-motor centres and the cardia muscle, producing a fall of blood pressure.

Respiration.—After an intravenous injection of erg toxine the respiration is increased both in force and fre

quency, possibly due to stimulation of the centre. (*See* Fig. 28). Large doses depress the centre when the respiration becomes slow and weak. Death occurs from asphyxia caused by the spasm of the muscles and weakness of the respiratory centre.

Uterus.—Ergot powerfully contracts the impregnated uterus of women and lower animals, specially when in labour, thereby expelling its contents. Hence it is a powerful ecbolic. This action is elicited within twenty to thirty minutes after administration by the mouth, and is due to ergometrine and ergotoxine. The contractions become more frequent than the normal ones and also more prolonged. In very large doses the contractions become not only very powerful and remain for a longer time but may become tonic. This may delay delivery and compress and asphyxiate the child, or even may cause rupture of the uterus. In doses given to produce uterine action, ergot has no effect on the blood pressure.

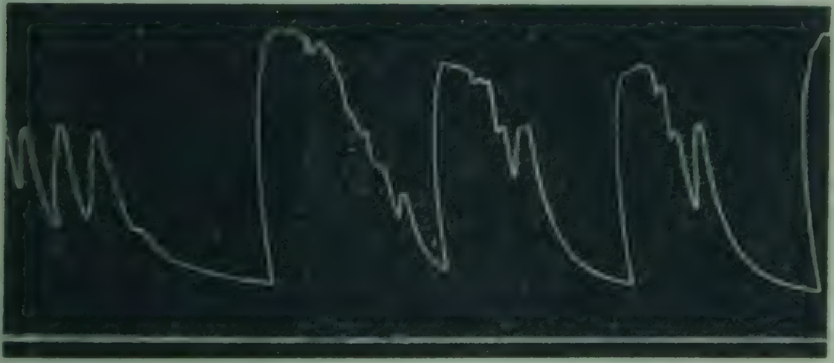


Fig. 29.—Showing effect of Ergometrine on Isolated Gravid Uterus of Guinea-pig suspended in Oxygenated Ringer.

Note—After a brief relaxation the individual contractions become larger, the period of relaxation being interrupted by numerous smaller contractions—a lasting effect on irritability of the uterus.

Eye.—After a momentary dilatation ergot powerfully contracts the pupil when injected intravenously. Dilatation is due to sympathetic stimulation and subsequent contraction is due to the direct action of ergotoxine on the iris, and is not counteracted by atropine.

Nervous system.—It has little effect on the brain. The highest centres are not affected by medicinal doses, not even by a single large dose. It produces changes of a sclerotic nature especially in the postero-external columns of the cord, and induces, when it is given for a long time, a train of symptoms known as "convulsive ergotism."

Secretion.—Secretion of saliva, sweat, milk and urine is diminished probably from the disturbance of the local blood-supply to the glands by the general vascular contraction.

Acute toxic action.—Acute poisoning is rare but sometimes large doses are taken to produce abortion. The symptoms are weak rapid pulse, tingling and itching of the skin, excessive thirst, gastro-intestinal irritation, uterine haemorrhage followed by abortion, unconsciousness and collapse. Abortion usually follows, but sometimes even in fatal cases there may be no abortion.

Chronic toxic action or Ergotism.—Poisoning by ergot rarely occurs when used medicinally, but it is very frequently seen amongst those who live on ergotised rye. This has occurred in epidemic form on the Continent of Europe. Mellanby holds that ergotism is due to the presence of a neurotoxin in the cereals and ergot and that deficiency of vitamin A acts as a contributory factor. It shows itself under one or other of the two forms described below.

1. **Gangrenous Ergotism.**—Various parts of the body, especially the extremities, suffer from imperfect blood-supply, owing to the constriction and thickening of the walls of the blood-vessels by ergotoxine thereby leading to a process of gangrene. It should not be mistaken for Raynaud's Disease.

2. **Convulsive Ergotism.**—In this variety, the patient first feels a sensation of itching, or tingling, and of insects crawling over the body, followed by a sensation of numbness and of local anaesthesia. These symptoms appear first in the hands and face, then spread over the body. The sensory impairment is soon followed by signs of motor irritation such as tonic contraction of the muscles, especially of the extremities ; and later on by the development of a staggering gait. Vomiting and diarrhoea often accompany this variety, and dimness of sight, loss of hearing, and epileptiform convulsions are occasionally present.

Ergometrine or ergonovine is mainly responsible for ergot effect. It is non-irritating and unlike the other alkaloids of ergot is rapidly absorbed from the stomach and rectum. Its action differs from that of the alkaloids of the ergotoxine group in that the effects are produced more rapidly, *i.e.* within 5 to 8 minutes when given by the mouth, 3 to 8 minutes when given intramuscularly, and within a minute when given intravenously. It contracts the uterus and the blood vessels by stimulating the sympathetic myoneural junctions, but unlike ergotoxine these are not subsequently depressed. It does not paralyse the adrenergic nerves or antagonise adrenaline. Its effects are less prolonged, lasting 3 to 4 hours, while that of ergotoxine lasts for 6 hours or longer. It has very little effect on other involuntary muscles, and when used for a prolonged period it has no gangrene producing properties, and its use is not followed by depression, headache and nausea so common with ergotoxine, ergotamine and ergoclavine.

It will appear that ergometrine resembles adrenaline and many sympathomimetic amines in its action on various structures. Perfusion of isolated rabbits heart shows acceleration.

Therapeutics

The chief use of ergot is in obstetric practice to increase uterine contraction. One school advocates its use

in all cases with weak contraction as an ecbolic, while others recommend its use only after the expulsion of the child, and will not use during labour, even at the late stage for fear of prolonging labour, or even causing death of the child from asphyxia. In any case the use of ergot as an ecbolic should be restricted only to those *cases of uterine inertia in which there is no mechanical obstruction to the passage of the child* ; otherwise the child's life may be endangered by the prolonged tonic contraction of the uterus, or if the resistance is too great it may cause rupture of the organ. If, however, it is used at all the dose should be small and well-regulated so that there cannot be any possibility of the tonic contraction. Ergot therefore is not used as a rule till after the expulsion of the placenta, when it ensures firm contraction of the uterus and prevents **post-partum haemorrhage.** In multiparas who are often subject to this sort of bleeding, it is a wise plan to administer ergot just after the expulsion of the foetus, or even before its birth if there be no contra-indication to its administration. In urgent cases ergometrine may be used intravenously ; or an injection of pituitary extract may be given along with a dose of ergot by the mouth so that the action of ergot will be manifest by the time the effect of pituitary passes off. It is often given combined with quinine during the puerperium to help involution of the uterus.*

As an internal *haemostatic* it has entirely lost its reputation ; for although it causes general constriction of the vessels this is attended with general rise of blood pressure. Its use in any form of internal haemorrhage other than uterine is irrational.

Ergot has been used in many other forms of bleeding from the uterus and sometimes with good results. For instance, it is used in menorrhagia, metrorrhagia and in bleeding from various forms of uterine fibroids.

ERGOTAMINAE TARTRAS. (Ergotam. Tart.). **Syn.**—Femergin.—Ergotamine Tartrate is the tartrate of an alkaloid obtained from certain species of ergot.

Characters.—Colourless crystals or white, crystalline powder. Readily soluble in water, the solution liable to become turbid ; tartaric acid gives a clear solution.

B. P. Dose.—1/60 to 1/30 gr. or 1 to 2 mg. single dose. By subcutaneous injection :—**1/240 to 1/120 gr. or 0.25 to 0.5 mg.**

Bellergal. (Not official).—Each tablet contains ergotamine tartrate 0.3 mg., *l*-hyoscyamine 0.1 mg., phenobarbitone 0.02 grm. Valuable sedative and in autonomic imbalance. In neurosis, migraine, menstrual disorders, etc.

* Ext. ergot. liq.	ms. 20
Quinin. hydrochlor.	grs. 4
Tinct. digit.	ms. 5
Sp. chlorof.	ms. 15
Aqua	ad. oz. 1

Pharmacology and Therapeutics

The action of ergotamine resembles that of ergotoxine except that its action on the uterus is more prolonged. It also paralyses the motor sympathetic nerve endings in larger doses though not so powerful as with ergotoxine. When administered subcutaneously in doses of $\frac{1}{120}$ to $\frac{1}{60}$ gr. (0.5 to 1 mg.) it causes constriction of the small vessels by acting directly on the muscles and slows the heart. Continued long, or in large doses, it causes persistent constriction of arteries with gangrene.

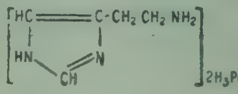
It is valuable in uterine haemorrhage specially when prolonged action is wanted. Apart from its uterine effect, it has been successfully used in the treatment of **migraine** and **recurrent headaches,** either given by the mouth in doses of 1 mg. ($\frac{1}{60}$ gr.) twice a day or by hypodermic injection in doses of 0.25 to 0.5 mg. ($\frac{1}{240}$ to $\frac{1}{120}$ gr.). It generally arrests the attack within an hour. Although oral use is generally ineffective it may be tried in mild cases. The tablets have also been used by sublingual administration and have been found to be more useful. In severe cases larger doses are necessary, but they may give rise to nausea and vomiting, tingling in the fingers and toes, muscular pain and weakness. Its action is believed to be due to abolition of the spasm of the cerebral vessels. It reduces the amplitude of contraction of the cranial vessels, and relief of pain follows when this occurs. Urticaria has been treated with ergotamine tartrate in 2 to 3 mg. ($\frac{1}{30}$ to $\frac{1}{20}$ gr.) doses given orally. It has also been used in Graves' disease.

HISTAMINAE PHOSPHAS ACIDUS

(Histam. Phosph. Acid.)

Syn.—Histamine Phosphate.

Source.—Histamine Acid Phosphate is the di-acid phosphate of histamine, 4-ß-aminoethylglyoxaline. Prepared by the action of phosphoric acid on histamine.



$C_5H_9N_3.2H_3PO_4$ . . . . . . Mol. Wt. 307·2

Characters.—Colourless crystals ; odourless. *Soluble* in 4.5 parts of water ; slightly soluble in alcohol (90 p.c.).

B. P. Dose.—1/120 to 1/60 gr. or **0.5 to 1 mg.** By subcutaneous injection.

Official Preparation

1. **Injectio Histaminae Phosphatis Acidi.—B. P. Dose.—1/120 to 1/60 gr.** or **0.5 to 1 mg.** N. B. When no strength is stated, 1/60 gr. in 15 ms. shall be dispensed.

Pharmacology and Therapeutics

Histamine occurs in extracts of all vegetable and animal tissues and is formed by the breakdown of proteins in the intestines by the bacterial action. As mentioned elsewhere (*see* page 304) the absorption of histamine or

some amine from the damaged tissue is the cause of shock, either surgical or from extensive burns. Guinea-pigs are more sensitive to it, while rabbits are insensitive. In the former the main effect is constriction of the bronchi, in rabbits constriction of the pulmonary vessels and in dogs hepatic veins.

Externally.—A solution of histamine (1 in 1000) applied to the skin and scarified produces what has been termed by Lewis a "triple response." This is characterised by a brief pallor, a definite flare and reddening due to vaso-dilatation and the formation of a local oedema or urticarial wheal. The flare does not appear if the nerves of the skin have degenerated but the oedema appears. This phnomenon has been ascribed to the liberation of a histamine-like substance. In susceptible persons subcutaneous or intramuscular injection of 0.5 to 1 mg. (1/120 to 1/60 gr.) will produce the same type of reaction over large areas of the skin.

Internally.— Administered by the mouth it is destroyed by the digestive juices, therefore very little effect is observed when given by this route. Some absorption probably takes place from the intestine (lower end of the ileum) and some clinical conditions are due to its absorption from damaged intestine. It is rapidly taken up by the tissues when injected and is more slowly destroyed by the enzyme *histaminase* which is present in high concentrations in the kidney and intestinal mucous membrane. It **contracts all plain muscles** including both the gravid and non-gravid uterus, bronchial and intestinal muscles.

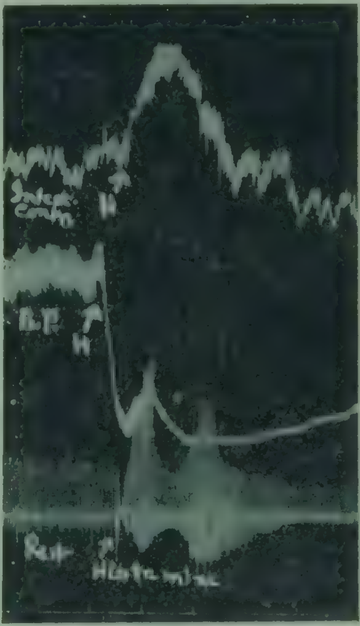


Fig. 30.—Dog under chloralose. Showing effects of small doses of histamine. Records from above downwards : intestinal contraction, blood pressure and respiration. Note—**profound and sustained fall of** blood pressure, increase of intestinal contractions and spasm of bronchial muscles, after a small dose given intravenously.

It causes fall of **blood pressure** and there is failure in the venous return due to generalised capillary paralysis. It also increases the permeability of the capillaries so that proteins and fluids escape from the vessels into

the tissue space which help still further to reduce the volume of circulating fluid. It causes contraction of the coronary arteries of ox, rabbit and man, but dilates, particularly the smaller ones, in cats.

Intravenous injection produces symptoms of shock of anaphylactoid type with asthmatic breathing due to contraction of the bronchial muscles and oedema of the mucous membrane.

In certain species of animals however, *e.g.* rabbits and guinea-pigs, it causes a rise of blood pressure, but in most animals including man the pressure falls from dilatation and increased permeability of the capillaries.

It increases the secretion of saliva, tears, gastric and pancreatic juice, from stimulation of the post-ganglionic parasympathetic fibres, but in man it increases the gastric secretion, specially the acid component in doses that have little or no effect on blood pressure. This effect is not antagonised by atropine. It has been used hypodermically to test the secretory response of the stomach in gastric disorders to distinguish *achylia gastrica* from chronic gastritis. If after giving a test meal an injection of 0.5 to 1 mil of 1 in 1000 solution does not provoke secretion of acid, achlorhydria is established.

It has been used hypodermically, by inunction or by ionization in the treatment of chronic rheumatoid arthritis, osteoarthritis and related conditions, the initial dose is 0.1 mg. increased by 0.05 mg. in normal saline daily till definite improvement is observed. Satisfactory dose is usually between 0.1 mg. ($\frac{1}{600}$gr.) and 0.5 mg. ($\frac{1}{120}$gr.) which is repeated 2 or 3 times weekly.

It has been used in certain specific types of **headache**, e.g. in histamine **cephalgia** and **migraine**, either subcutaneously or intravenously. The dose varies from 0.1 to 0.5 mil of 1 in 1000,000 solution. Similar amounts of 1 in 100,000 solution given every two or three days maintain relief from symptoms. This may be supplemented by sublingual administration of 1 to 2 drops of a 1 in 10,000 or a 1 in 1,000 solution, once or twice daily.

Histidine Hydrochloride. (*Not official*). Syn.—Larostidine.—A monohydrochloride of the base—histidine, an amino-acid corresponding to histamine.

Dose.—3 grs. or 0.2 grm. in 4 p. c. solution by subcutaneous or intramuscular injection daily for three weeks.

ACTION AND USES.—Histidine is the constituent of most of the simple proteins contained in such food-stuffs like meat, egg, fish etc. It has been used in the treatment of peptic ulcer on the unsubstantiated theory of Aron and Weiss that such ulcers are due to a deficiency of amino-acid and that administration of histidine corrects that deficiency. Relief from symptoms follows in 2 to 6 days. The advantage claimed for this treatment is that the

patient goes through his usual routine work without any restriction in diet. It has not proved a success and cases are being recorded of disappointing relapses. Moreover, daily injections, expense and reactions which sometimes occur are also drawbacks for the use of this remedy.

Antihistaminic Drugs

Dale and Laidlaw have shown that injection of histamine intravenously produced symptoms similar to anaphylactic shock. Histamine is a natural constituent of many tissues of the body and in shock it is liberated in the blood and lymph to produce the symptoms. Since all the symptoms of anaphylactic shock may not be due to histamine itself, it has been suggested that other substances like acetylcholine, heparin are also liberated and this group of liberated substances, responsible for shock, is called *H-substance*, of which histamine is the most important.

Attempts have been made to counteract this H-substance and antihistamine therapy aims at (a) development of tolerance to histamine by a series of injections of histamine or histamine diphosphate or some other form of histamine in minute doses ; and (b) administration of such drugs which will neutralise the effects of histamine in the body.

The enzyme *histaminase* destroys histamine in *vitro* but whether it acts in *vivo* or can escape destruction in the stomach and intestine is doubtful. For all practical purposes, substances which counteract the effects of histamine by their own special action, are generally used. Thus adrenaline, though very useful for this purpose possesses other important actions ; similarly, atropine is also a valuable antihistaminic substance but its effects on the parasympathetic nervous system reduce its usefulness for the former effect. Systematic search for substances having specific antihistaminic effect has been made and it has been shown that certain ethylenediamine derivatives possess antihistamine properties.

All these drugs possess more or less similar therapeutic properties and have been used in different allergic diseases. They antagonise all the actions of histamine in the body, i.e. prevent fall of blood pressure and the increase of capillary permeability ; relax smooth muscles and counteract the symptoms and signs of anaphylactic shock, although there are individual variations of their actions, some being more powerful than others. But they do not inhibit the secretion of hydrochloric acid induced by histamine. These effects are generally produced (1) by exerting pharmacological actions which are directly opposed to those of histamine, e.g. sympathomimetic drugs, viz. adrenaline causes relaxation of the smooth muscles of the intestine and bron-

chioles; (2) by preventing or opposing the actions of hista-mine. They block or obliterate the activity of histamine in the living tissues; (3) by destroying or neutralising hista-mine by some direct chemical action.

It has been suggested that these drugs act by substrat competition, i.e. they combine with some receptor com-pound in the tissues and thus prevent histamine from com-bining with the same receptor. Others believe that th mode of action is more complicated than merely a simp competition for a receptor.

Contrary to the general belief that they are highl specialised substances as pure antihistaminic agents the possess certain other side-actions, namely (1) they are *loca anaesthetics*, some like mepyramine (neoantergan) is abou three times more powerful than procaine; (2) posses *quinidine-like action* and prolong the refractory period o the heart muscle; (3) they have *anti-acetylcholine action* i.e. produce dryness of the mouth and counteract the effec on the smooth muscle including muscles of the vessels; (4 *anti-adrenaline-like action*; and (5) action on the *centr nervous system* producing drowsiness and central analges effect. It will be seen that these compounds also share pro perties with drugs like atropine, pethidine, procaine an quinidine.

All these drugs are used as anti-allergic agents in th treatment of hay fever, urticaria, contact dermatitis, vaso motor rhinitis, drug sensitiveness, histamine cephalgi asthma, angioneurotic oedema, serum reaction, pruritu etc. with varying degrees of success.

Of the different antihistaminic drugs mepyramine, pro methazine and pyribenzamine are more effective in the pre vention of histamine induced broncho-spasm and clinic allergic diseases than, benadryl and antistin.

Antihistaminic drugs do not prevent the developmen of sensitization nor do they interfere with presumed antigen antibody reactions which underlie the production of allerg manifestations. At best they should be regarded a palliative.

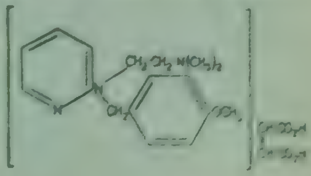
Administration.—These drugs are usually administere by the mouth, although they may be administered parente ally by subcutaneous, intramuscular or slow intraveno injection. They are fairly rapidly absorbed from th gastro-intestinal tract, highest reactions occurring aft 1½ to 4 hours and persists for 4 to 6 hours. Promethazi however possesses a very prolonged action. It has bee found that the time of decay from full action to half acti varies as follows: promethazine, 19½ hours; mepyrami 5 hours 10 minutes; antistin 3½ hours; pyribenzami 3¼ hours.

MEPYRAMINAE MALEAS

(Mepyramin. Maleas.)

Syn.—Neoantergan; Anthisan.

Mepyramine Maleate is the acid maleate of *N*-*p*-methoxybenzyl-*N'N'*-dimethyl-*N*-2-pyridylethylenediamine. A white or creamy-white powder, having not more than a slight odour; taste, bitter. *Soluble* at 20° in about ·5 part of water, in 2.5 parts of alcohol (95 p.c.) and in 1.5 parts of chloroform.



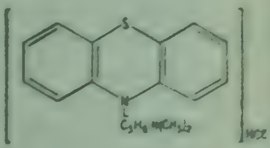
B. P. Dose.—5 to 12 gr. or 0.3 to 0.8 grm. *daily, in divided doses.*

Action and Uses

Mepyramine is an antihistaminic drug and sufficiently non-toxic and is well tolerated in clinically effective doses. It is also a local anaesthetic being three times as potent as procaine, possesses quinidine-like action on the auricle. It antagonises the effects of histamine on the blood pressure, bronchi and intestine, but has no effect on its action on the gastric juice. It should be administered by the mouth and the initial dose should be 0.1 grm. ($1\frac{1}{2}$ gr.) three times a day to be slowly increased as required to a maximum of 0.8 grm. or 12 gr.

Common side effects are sleepiness, mild headache, nausea and diziness.

PROMETHAZINAE HYDROCHLORIDUM. (Promethazin. Hydrochlor.). Syn.—Phenergan.—Promethazine Hydrochloride is the hydrochloride of *N*-(2-dimethylamino-*n*-propyl) phenothiazine. Contains 10.8 to 11.2 p.c. of Cl, and 8.5 to 8.9 p.c. of N. A white or slightly creamy powder, with not more than a silght odour; taste, very bitter. *Soluble* at 20° in 0.6 part of water, in about 9 parts of alcohol (95 p.c.) and in 2 parts of chloroform.



B. P. Dose.—2/5 to 1½ gr. or 25 to 75 mg.

Action and Uses

Promethazine is seven times as powerful as mepyramine and the effect lasts longer than any of the other antihistaminic drugs. It is therefore used in all cases where prolonged action is desired and where other antihistaminic drugs either proved unsuccessful or impracticable owing to the need of higher dosage and more frequent administration. Ordinarily oral use is enough and well tolerated if the dose is not exceeded. Usually 25 mg. (2/5 gr.) is sufficient to give relief but sometimes this may not control the symptoms when two such doses or tablets may be given preferably at bedtime.

NON-OFFICIAL ANTIHISTAMINIC DRUGS

Diphenhydramine. Syn.—Benadryl.—It is Benzhydryl-2-dimethylaminoethyl ether.—It has three important properties: It

Lessen

alleviates (a) bronchial spasm caused by histaminic or anaphylactic shock; (b) counteracts the vaso-depressor effects of histamine; and (c) relieves the spasm of smooth muscles. It has therefore been used in different allergic conditions. In acute urticaria the result is better than in chronic cases where it has to be continued for a prolonged period. Both benadryl and pyribenzamine are effective in urticaria from penicillin in doses of 50 to 100 mg. by the mouth three times a day.

Benadryl does not give relief in asthma in all cases, and it has been reported to have aggravated acute attacks in some cases. It is best used for prevention of attacks. It may be used to counteract the vaso-depressor effect of histamine and to relax smooth muscle.

Administration.—It may be used orally, intramuscularly, 1/6 gr. (10 mg.) in 1 mil, but it is locally irritating. Intravenously, 1 gr. (60 mg.) in 100 mil of normal saline and administration taking 10 minutes.

Dose.—The dose for adult is 50 to 100 mg. (3/4 to 1½ gr.) daily. This dose is increased by 50 mg. (3/4 gr.) on each successive day till a maximum of 600 mg. per day, if necessary, is reached. The dose should be taken after each meal four times a day; the last dose being taken before retiring.

For children the maximum dose is 2 mg. (1/30 gr.) per pound of body weight.

Toxic effects.—Drowsiness and lassitude. These are overcome by giving black coffee, caffeine, amphetamine or ephedrine. Dizziness, visual disturbance, epigastric distress, sometimes nausea and vomiting, frequent micturation and mild inco-ordination have also been recorded.

It should be given with caution to persons who have taken a hypnotic and to aspirin-sensitive patients.

Tripelennamine. **Syn.**—Pyribenzamine.—It is *N*-Benzyl-*N'N'*-dimethyl-*N*-2-pyridylethylenediamine.—It is given in same doses and in the same conditions where benadryl is indicated. It produces the same toxic effects as benadryl but to a lesser degree.

Antazoline. **Syn.**—Antistin; Histostab.—It is 2-*N*-Benzyl-anilinomethyliminazoline.—It is a powerful antihistaminic drug and may be used in urticaria, eczema, neurodermatitis, and in all allergic and anaphylactic reactions, serum sickness, etc. The usual **dose** is 0.1 grm. or 1½ gr. (one tablet) three times a day. Children 1/4 to 1/2 tablet three times a day. By intramuscular or slow intravenous injection, 1/2 to 2 mil (2 mil contains 0.1 grm.).

Phenindamine. **Syn.**—Thephorin.—1:2:3:4-Tetrahydro-2-methyl-9-phenyl-2-azafluorene. It is well tolerated by children; only disadvantage is dryness of the mouth, constipation, sleeplessness or drowsiness. **Dose.**—25 mg. (2/5 gr.) in tablets. **Average daily dose,** 100 mg. (1½ gr.).

Chlorcyclizine. **Syn.**—Histantin.—(±)-1-(*p*-chlorobenzhydryl) 4-methyl-piperazine.—A new type antihistamine chemically unrelated to other antihistaminic agents. Its action is more prolonged, lasting 12 to 16 hours and except drowsiness in about 5 p.c. of cases is relatively free from side-effects. **Single daily dose** is 50 mg. (3/4 gr.) may be increased to 100 mg. (1½ gr.).

HYDRASTIS RHIZOMA, B. P. C. **Syn.**—Golden Seal.—The dried rhizome and roots of *Hydrastis canadensis*. It contains alkaloids (1) *Berberine*, 1.5 to 4 p.c. (2) *Hydrastine*, 2.5 p.c., and (3) *Canadine*.

NON-OFFICIAL PREPARATIONS

1. **Extractum Hydrastis Liquidum, B. P. C.**—1.9 to 2.1 p.c. hydrastine. *Dose.*—5 to 15 ms. or 0.3 to 1 mil.

2. **Hydrastinae Hydrochloridum, B. P. C.**—A white or creamy white powder. Odourless and soluble in water. *Dose.*—1/4 to 1 gr. or 16 to 60 mg.

PHARMACOLOGY AND THERAPEUTICS

Internally.—Being bitter, it promotes appetite and digestion, and stimulates gastric and intestinal secretion and peristalsis. It is therefore a **stomachic** and **laxative.** It contracts the unstriped muscular fibres of the arteries and those of the uterus, hence it is a **haemostatic** and **ecbolic**, though the contractions are not so strong as those produced by ergot. The action is direct on the uterine muscle. Hydrastine is a mild febrifuge. On the nervous system its action resembles strychnine, and it increases the reflex excitability and slightly stimulates the vagus, vaso-constrictor and respiratory centres. In large doses it causes convulsions. On the circulation its effects are too uncertain to be of any use therapeutically.

It is one of the most useful remedies we have for chronic gastric and **intestinal catarrh,** especially of chronic alcoholism. It has been largely employed in arresting **haemorrhages,** especially **uterine.** In short it may be used in all cases where ergot is indicated. It is however a *weak substitute for ergot* and cannot replace either ergot or pituitary in the treatment of post-partum haemorrhage. As an **antiperiodic it is inferior to quinine.**

INJECTIO PITUITARII POSTERIORIS

(Inj. Pituit. Post.)

Syn.—Extractum Pituitarii Liquidum; Pituitary (Posterior Lobe) Extract; Pituitary Extract; Posterior Pituitary Injection; Pituitrin.

Source.—Injection of Pituitary (Posterior Lobe) is a sterile aqueous extract of the posterior lobe of pituitary bodies of oxen or other mammals. Contains 10 units (oxytocic) per millilitre.

Characters.—A clear, colourless liquid with a faint odour.

Composition.—(1) *Oxytocin* or *pitocin*, oxytocic principle, causes contraction of the uterus and without any effect on blood pressure. (2) *Vasopressin*, or *pitressin*, causes rise of blood pressure and vaso-constriction. Causes both diuresis and anti-diuresis, and relieves post-operative intestinal stasis.

B. P. Dose.—By subcutaneous or intramuscular injection :—**3 to 8 ms. or 0.2 to 0.5 mil. (2 to 5 Units).**

Injectio Oxytocini. **Syn.**—Oxytocin; Pitocin.—Injection of Oxytocin is a sterile aqueous solution containing the oxytocic principle from the posterior lobe of the pituitary bodies of oxen or other animals. **A clear, colourless, liquid.**

B. P. Dose.—By subcutaneous or intramuscular injection :—**8 to 15 ms. or 0.5 to 1 mil. (5 to 10 Units).**

Injectio Vasopressini. **Syn.**—Vasopressin; Pitressin.—Injection of Vasopressin is a sterile aqueous solution containing the pressor and antidiuretic principles from the posterior lobe of the pituitary bodies of oxen or other mammals. A clear colourless liquid.

B. P. Dose.—By subcutaneous or intramuscular injection :—**8 to 25 ms. or 0.5 to 1.5 mil. (5 to 15 Units).**

PHARMACOLOGY

Heart and blood-vessels.—After an intravenous injection of the extract there is a rise of **blood pressure.** A second injection often has no effect if given shortly after the pressure has returned to its normal height. The effect, although not so sudden as adrenaline, is more prolonged and lasting and is due to direct stimulation of the muscles of the arteries and not the myoneural junction of the

vaso-constrictors. The arterial pressure begins to rise within a minute and may last for about half an hour. It constricts the coronary, pulmonary and cerebral arteries. In man the effect on blood pressure is variable ; sometimes

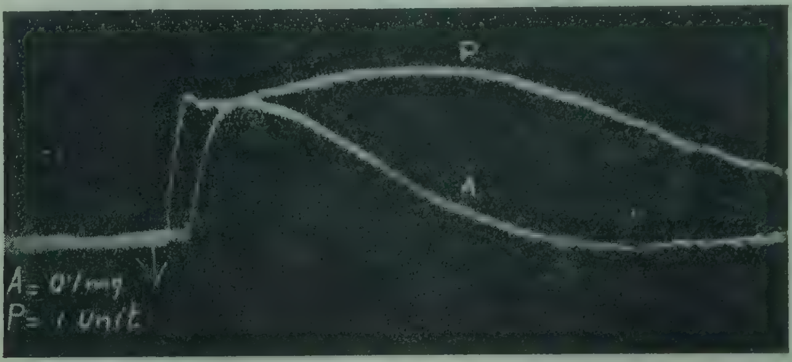


Fig. 31.—Anaesthetised cat. Showing effects of Pituitrin (P) and Adrenaline (A) on blood pressure in contrast.

there is no rise ; often however there is a fall although the capillaries are constricted, possibly due to slowing of the heart from reflex vagus stimulation and diminished nutrition and oxygenation due to coronary constriction. Removal of the gland causes loss of tonus of the capillaries of the frog which is restored by the administration of the extract. It is possible that the pituitary secretes a substance which maintains the normal tone of the capillaries and that substance is vasopressin.

It **slows the heart** due partly to stimulation of the vagus centre from increased blood pressure and partly from its direct action on the cardiac muscle. The rate is quickened during the fall of pressure. Whether the rate is slowed or quickened the output of the heart is diminished and the **pulmonary pressure falls.** In intact animals the heart muscle is weakened from diminished oxygen supply from coronary constriction.

Absorption.—It is not absorbed by the unbroken skin and administered by the mouth it is destroyed by the digestive juices. Given per rectum or applied to the nasal mucosa it is sufficiently absorbed to elicit antidiuretic effect and contraction of the uterus. Full therapeutic effects are elicited when given subcutaneously or intramuscularly. The pressor effect is well marked after intravenous use.

Alimentary canal.—It decreases salivary, gastric, pancreatic and intestinal secretions. Both subcutaneous and intravenous doses have a marked effect on the intestinal muscles causing increased tone and peristalsis. This effect is due to vasopressin, and is antagonised by atropine. Quigley and Barnes have however shown that the gastro-

intestinal movements are depressed by both the active principles in intact animals. The effect on excised strips of intestine is that of stimulation, though variable and complex.

Kidneys.—It first causes **diuresis** which is the result of passive dilatation of renal vessels and high blood pressure; but this is followed by **diminished secretion** which is of longer duration. In man and in unanaesthetised animals it diminishes the secretion specially when polyuria is present, as in cases of diabetes insipidus. The antidiuretic action is normally due to vasopressin and will reduce diuresis in doses too small for circulatory effect. This antidiuretic hormone acts directly on the tubule, and helps reabsorption of water by stimulating the epithelium. It is possible that the posterior pituitary regulates the flow of urine and probably has no influence on the circulation under physiological conditions. Richards has pointed out that the antidiuretic effect is helped by the contraction of the glomerular capillaries. There can be no doubt that the general constriction of the vessels which is also shared by the glomerular capillaries contributes to the antidiuretic effect as this lessens the filtration surface.

It is antagonistic to insulin, as direct stimulation of the gland or injection of the extract is followed by hyperglycaemia and glycosuria (Dale and Burn). This antagonism is not a direct chemical one but is performed through the intermediary of the liver. Both oxytocin and vasopressin produce this effect but which one will produce the greater effect depends largely on the species. Thus in rabbits and in dogs oxytocin produces greater hyperglycaemic action. The vasopressin moiety empties the glycogen reservoirs in the liver, while insulin stores up dextrose as glycogen. It increases the excretion of chlorides.

Female generative organs.—Pituitary by virtue of oxytocin causes powerful contraction of the uterus, whether pregnant or not, by acting on the uterine muscle. In guinea-pigs it causes contraction of isolated virgin uterus. Some hold that on the human uterus its action is only elicited during labour. But this is doubtful and pregnant human uterus whether in labour or not shows marked contraction. The effect is more rapid (occurring within 2½ minutes) and lasts for a shorter time (less than an hour) than ergot. It differs from adrenaline in that it acts on all animals and has no effect on the nervous mechanism. This action is more marked than its effect on the intestine and is elicited whether it is given hypodermically or intravenously. It is a galactogogue and does not increase the amount of milk secreted, but only helps the expulsion from increased contraction of the unstriped muscles of the mammary glands

Respiration.—Respiration is first strengthened and then becomes shallow and slow. After repeated injections no effect is produced. Sometimes bronchial muscles are contracted due to the presence of histamine as an impurity. Pure preparations have no such effect.

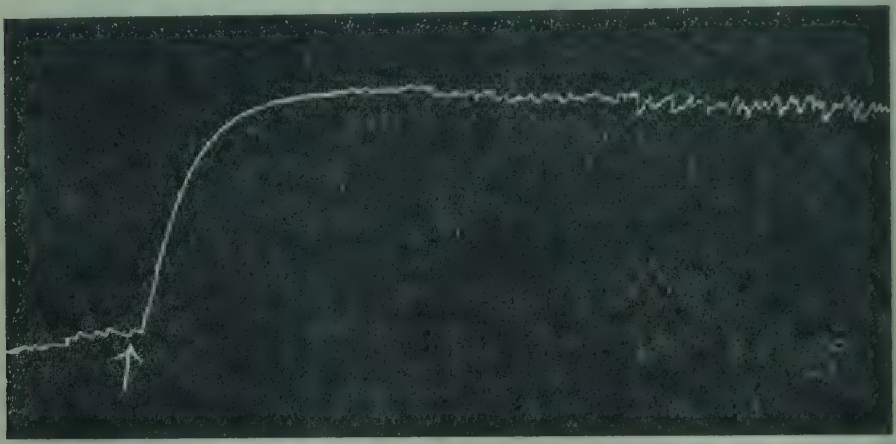


Fig. 32.—Effect of Pituitrin on the Isolated Uterus (non-gravid) of Guinea-pig suspended in oxygenated Ringer's solution. Contraction is indicated by the upward movement of the lever.

The actions of pituitrin and adrenaline are compared in the following table :—

Pituitrin	Adrenaline
1. Causes rise of blood pressure, action not so rapid and the effects last longer (*see* Fig. 31).	Causes rise of blood pressure, action more rapid, and the effects of shorter duration.
2. Slows and weakens the heart.	Accelerates and strengthens the heart.
3. Constricts the coronary and pulmonary vessels.	Dilates coronary vessels.
4. Acts as a diuretic from passive dilatation of the renal vessels followed by oliguria.	Constricts renal arteries.
5. Stimulates the intestine, bladder and pregnant uterus.	Inhibits.
6. Acts directly on the muscle fibre.	Stimulates the sympathetic nerve-endings.

Therapeutics

The chief use of pituitrin (either posterior lobe extract or injection of oxytocin) is in obstetric practice and it is the most valuable means of strengthening weak labour pains and arresting post-partum haemorrhage. Its use therefore has been suggested in the second stage of labour when it helps expulsion of the foetus. Since it stimulates uterine contraction during puerperium it is used preliminary to the use of ergot after the expulsion of the placenta or just before its expulsion to ensure firm contraction and arresting post-partum haemorrhage. Its use however should be restricted to those cases of uterine inertia where there is no mechanical obstruction to the passage of the

child. When used to strengthen labour pains it may, through powerful contraction, actually delay the birth of the child or may cause asphyxia, premature separation of the placenta, or even injury to the soft parts.

For its powerful action on the blood pressure pituitary extract is largely used in the prevention and treatment of shock, specially occurring during the anaesthesia of **severe surgical operations.**

Because it causes contraction of the intestinal muscles, it is used in tympanites and intestinal paralysis which may occur after surgical operations, or as a complication of some acute infection. It is doubtful whether it does good in all cases, and in advanced cases of intestinal paralysis following an infection, it has often been found to fail. Its use has been suggested in gastric ulcer and hyperchlorhydria on the idea that it decreases gastric acidity by increasing the excretion of urinary chlorides, thereby diminishing the chloride content of the blood.

As pituitary is an outgrowth of the nasal mucosa, it might be absorbed by spraying into the nose, or from plugs of cotton wool soaked in the solution of the extract and inserted high up into the nasal cavity. This method of treatment has been used with success in diabetes insipidus. In fact the administration of the posterior lobe extract diminishes polyuria, relieves thirst and increases concentration of the urine. To be effective it should be given either as *intranasal spray* or *hypodermically*. Because of its antagonism to insulin, it may be used to counteract hypoglycaemia following an overdose of insulin.

Injection of pituitrin (0.5 to 1 mil) is of value in the early stage of **herpes zoster** when it allays pain and shortens the duration of eruption. The mechanism of its action is however obscure.

The whole gland pituitary extract is useful in obesity of pituitary origin which is characterised by deposition of fat around the girdles and commonly occurs in children and adolescents. It is usually given in combination with thyroid extract $\frac{1}{4}$ gr. each and then working up to a point at which the patient loses one to two pounds a week. It has however failed to reduce any weight when given to carefully selected cases for prolonged periods.

Class B : Sex stimulating Hormones and Sex Glands

PITUITARY (ANTERIOR LOBE) EXTRACT

The anterior lobe of the pituitary gland, through its hormones, appears to influence nearly all the physiological processes of the vertebrate animal, some more profoundly than others. The important influence is manifest on the process of growth and the ovarian and testicular activity. So far as is known the nervous system is least influenced. Removal of the gland produces important changes in the gonads, the suprarenal cortex, the thyroid and the growth,

and possibly the parathyroid and the pancreas. Similarly its injection will accelerate growth in the young animal, or cause the fully grown animal to grow further, produce precocious sexual development in female rats and will bring on menstruation in monkeys. It produces the above functions through several hormones.

It exhibits two types of cells, *viz.*—(1) *Chromophobe cells*, without any special affinity for dyes, possibly influence the development of secondary sex characters ; (2) *chromophil cells*, which stain readily and have been subdivided according to the character of the granules into *eosinophil cells* and *basophil cells*, the former yields the growth-promoting hormone and the latter helps in the production of sex hormones.

It controls the activity of the gonads in both male and female by means of the gonadotrophins or gonadotrophic hormones, known as follicle stimulating hormone (FSH or prolan A) and the luteinizing hormone (LH or prolan B). These are now known respectively as gonadotrophin I and gonadotrophin II. They are responsible for the development of male and female reproductive system. Similar principles are found in the urine of pregnant women and pregnant mares, in the serum of pregnant mares and also from the chorionic tissue. Since these differ in certain respects from the hormones derived from the anterior pituitary they are known as *anterior pituitary-like hormones.*

A. Gonadotrophic or sex-stimulating hormones

The *follicle stimulating hormone* stimulates the ovarian follicles and helps them to ripen and ovulate with liberation of the hormone oestradiol or oestrone, which sets up proliferative changes in the uterine mucosa and maturation of the uterus ; the *luteinizing hormone* produces luteinization of the follicular walls and rapid formation of the corpora lutea and fixation of the ovum, hypertrophy of the uterus and increased lactation.

B. Anterior pituitary-like gonadotrophic hormones from other sources

1. *From human pregnancy urine or the chorionic part of the placenta.*—This gonadotrophic factor is obtained from human pregnancy urine or the placenta in the form of luteinizing hormone, the follicle stimulating factor being absent. The anterior pituitary-like substance of the placenta and the gonadotrophic principle of pregnancy urine are identical, i.e. the gonadotrophic principle in the urine of pregnancy is derived not from the pituitary but from the placental (chorionic) tissue. It possibly serves to supplement the action of the pituitary in maintaining the growth of the corpus luteum during pregnancy. The largest amount of this luteinizing factor being secreted about the 50th to 60th day following the last menstrual period.

2. *From pregnant mares' serum.*—This differs in several respects from the factor derived from human pregnancy urine. And although this is present in the serum of pregnant mares it is not excreted in significant amounts in the urine even when its concentration in the serum is at its highest. This hormone is secreted by the endometrium and chorionic epithelium, is far more complete in its gonadotrophic effects than the one obtained from the pregnancy urine. It resembles more in its effect the hormone derived from the pituitary anterior lobe, and therefore is a better therapeutic agent than the one obtained from pregnancy urine.

GONADOTROPHINUM CHORIONICUM. **Syn.**—Antuitrin-S; Glanduantin; Gonan; Pregnyl; Prolan.—Chorionic Gonadotrophin is a sterile preparation containing gonad-stimulating substance obtained from the urine of pregnant women.

Characters.—A white, or fawn powder. *Soluble* in water.
B. P. Dose.—By intramuscular injection :—100 to 500 Units.

OFFICIAL PREPARATION

1. **Injectio Gonadotrophini Chorionici.**—**B. P. Dose.**—By intramuscular injection :—100 to 500 Units.

Gonadotrophinum Sericum. Syn.—Antostab; Luteoantin; Gestyl; Gonadin.—Serum Gonadotrophin is a sterile preparation containing the follicle-stimulating substance obtained from the serum of pregnant mares.

Characters.—A white powder. *Soluble* in water.
B. P. Dose.—By intramuscular injection :—200 to 1000 Units.

OFFICIAL PREPARATION

1. **Injectio Gonadotrophini Serici.**—**B. P. Dose.**—By intramuscular injection; —200 to 1000 Units.

N. B. The label should indicate the number of Units contained in the sealed container. Should be used immediately after preparation.

NON-OFFICIAL PREPARATION

1. **Ambinon A.**—Gonadotrophic and Thyrotrophic. Each 1 mil ampoule contains 50 rat units of pituitary gonadotrophic and 100 to 300 guinea-pig units of thyrotrophic hormone. Also contains 100 i. u. of Pregnyl powder to be dissolved in the former just before using. **Ambinon B.**—Contains only the ambinon solution.

ACTION AND USES

The presence of oestrogenic hormone in the urine of pregnant women forms the basis of the well-known Aschheim-Zondek test for pregnancy. It is done by injecting 0.2 to 0.4 mil of the urine into immature female mice twice daily for three days when the mice are killed, the ovaries will show blood-filled follicles and also corpora lutea. This test can be obtained when the pregnancy has only lasted for less than a month and remains positive for twelve days after delivery.

Treatment with anterior pituitary gonadotrophic hormone is done with the preparation either from human pregnancy urine or from pregnant mare's serum. As mentioned before the latter preparation has a more complete gonadotrophic action than the one prepared from human pregnancy urine, and therefore much wider field

of usefulness. The indications are, sterility in the mal when due to azoospermia, in the female when due to ovaria insufficiency, infantilism and cryptorchidism.

It is supposed to act as a specific in adiposo genit dystrophy, a disease characterised by retarded sexu development, adiposity, lethargy and deficient vital fun tions (Frohlich's syndrome). It is also of value in atrop of the anterior lobe. Dried gland has been used by th mouth and also an extract hypodermically, but it is doub ful, if when given by the mouth, it produces any marke improvement. It has been used in sexual infantilism wit amenorrhoea and delayed puberty, functional sterility a dysmenorrhoea and delayed menstruation due to deficienc of the corpus luteum. In larger doses it has been used i menorrhagia and metrorrhagia and in the treatment o climacteric haemorrhage and threatened abortion.

It has been used with success in undescended testi on the idea that it would stimulate both the developmen and the descent of the imperfect organ. It is particularl useful in those cases in which the testis has passed throug the canal and is occupying the upper reaches of the scrotum It is possible that it increases the bulk of the testis and the descent is due to gravity. The treatment consists of 100 to 500 or 1000 units twice weekly for three weeks or daily injections for 30 days. It may cause premature development of sex organs in children both male and female.

All these are administered intramuscularly, and since they are protein in nature, it is necessary to test for allergic reaction specially when preparation from mare's serum is used.

Other Anterior Pituitary Hormones

Lactogenic Hormone.—This hormone influences the growth of the mammary glands during pregnancy and is responsible for the secretion of milk. The hormone, *prolactin*, has been isolated as a crystalline substance, and has been used clinically with success in women in whom the function is failing.

Growth Promoting Hormone.—Its absence, from removal of the gland, or its insufficiency, is followed by infantilism. While its excessive secretion is followed by acromegaly and gigantism.

Thyrotrophic Hormone.—Its loss or insufficiency is followed by atrophy of the thyroid with reduction of the basal metabolic rate which is prevented by the injection of the extract of the anterior pituitary. The administration of this hormone to animals is followed by exophthalmos and hyperthyroidism.

Diabetogenic and Ketogenic Hormones, which influence the metabolism of carbohydrates and fats.

Adrenotrophic Hormone, stimulates the adrenal cortex and its removal or absence is followed by atrophy of the cortex.

Besides these, other hormones influence protein metabolism and parathyroid.

Sex Glands

The sex glands (testes and ovaries) also known as the *gonads* are the primary organs of sex, furnishing the male or female se

cells (spermatozoa or ova) upon which the ultimate maleness or femaleness of the animal depends.

Sexual life is regulated by different hormones, *viz.*, the bi-sexual gonadotrophic hormones and the lactogenic hormone of the anterior pituitary gland, and the analogous gonadotrophic hormones of the chorion and the placenta. The sex glands themselves produce hormones but they remain dormant until stimulated by the gonadotrophic hormones of the anterior pituitary, etc. During childhood, small amounts of pituitary gonadotrophic hormones keep up a limited output of oestrogenic and testicular hormones which help gradual development of the genital apparatus. At puberty, the output of these hormones increases with corresponding activation of the sex glands and increased formation of theelin and androsterone as the case may be, causing rapid development of secondary sex characters. After maturity, the female cycles appear which consist of the ripening of the follicles and mobilisation of oestrogenic substances with the associated morphological effects, luteinization and production of progesterone.

I. **The Ovary.**—The ovary performs several diverse functions. It is responsible for the development of the secondary sexual characters of women. Menstruation depends upon their proper functioning, while their removal after puberty is followed by atrophy of the uterus, vagina and the external genital structure and cessation of menstruation. It also helps to fix the embryo into the uterus until it is sufficiently developed to survive birth and to maintain an independent existence. The cyclic activity of the ovary corresponds with the cyclic changes in the uterus and vagina, and this is regulated by the anterior pituitary gonadotrophic hormones. Gonadotrophin I causes maturation of the follicles and liberation of oestrogenic substances producing changes in the animals known as oestrus. The luteinizing hormone (gonadotrophin II) helps development of the corpus luteum which persists for about ten days and secretes progesterone and oestradiol. After this period the corpus luteum regresses and the supply of ovarian hormone is cut off.

The different hormones isolated from the ovary are (*a*) *oestrin*, also known as follicular hormone or female sex hormone; and (*b*) *corpus luteum hormone* or *progesterone* concerned in the prevention of ovulation and is largely antagonistic to oestrin. Apart from progesterone all hormones are bi-sexual in action. Thus testosterone will restore the structure of the atrophied uterus and vagina of an ovariectomised female, and oestrin will cause enlargement of the seminal vesicles and prostate.

The main steroid hormones of importance in the body are oestradiol, progesterone, testosterone and deoxycortone from adrenal cortex.

Oestrin.—It is a term applied to hormones present in the ovaries, placenta, foetal membranes and liquor amnii, and the urine of pregnant women. It can also be obtained from the *testes* and other tissues of the male. It has been isolated in pure crystalline form.

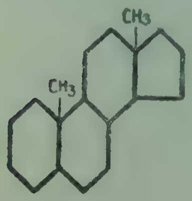
The unit is defined as the specific oestrus-producing activity in 0.0001 mg. of the standard preparation which is a hydroxyketonic form of the hormone obtained from urine of pregnancy, and kept at the National Institute of Medical Research, London. The oestrus-producing activity is the power of producing in adult female rats or mice, completely deprived of their ovaries, the cellular changes in the vaginal secretion characteristic of normal oestrus.

Chemistry and Sources of Oestrogenic Substances

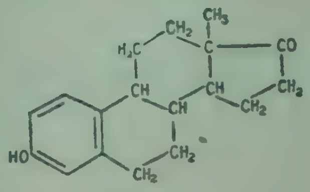
Substances possessing the biological properties of oestrin can be divided into two groups, *viz.*—

(a) Naturally occurring oestrogens

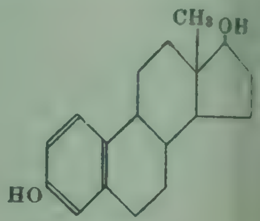
Doisy (1929) suggested the name theelin to the crystalline oestrin he isolated from pregnancy urine. Others call it oestrone or *ketohydroxyoestrin*, as it contains a *keto* and a *hydroxyl* group. Another active substance, theelol was obtained shortly afterwards from pregnancy urine. It was also designated *oestriol* or *trihydroxyoestrin*, as it contains three hydroxyl groups and ketone. Oestriol ($C_{18}H_{24}O_3$) contains one more molecule of water than oestrone ($C_{18}H_{22}O_2$) and is transformable to the latter by dehydration in vacuo by $KHSO_4$.



Sterol mecleus



Oestrone



Oestradiol

Reduction of ketone group in oestrone to a hydroxyl group results in the formation of dihydroxyoestrin, known as oestradiol, which is five times more active than oestrone. Oestradiol was obtained from sow ovaries and pregnant mares' serum, and it is believed to be the naturally occurring oestrus principle ; oestrone and oestriol being degradation products.

Esters.—Various esters of oestradiol and its derivatives have been tried and the replacement of the hydroxyl group (in the three positions) in dihydroxyoestrin (oestradiol) with benzoic acid leads to the formation of oestradiol benzoate which possesses a very prolonged action. Similarly, oestradiol dipropionate possesses a still greater and more prolonged action.

OESTRONUM. (Oestron.). Syn.—Ketohydroxyoestrin ; Theelin. —Oestrone is 3-hydroxy-17-keto-$\Delta^1 : {}^3 : {}^5$-oestratriene and may be prepared from the urine of certain mammals.

Characters.—Colourless crystals ; odourless. Very sparingly *soluble* in water, slightly soluble in dehydrated alcohol and in solvent ether ; soluble in chloroform, acetone, benzene, fixed oils and in aqueous solutions of alkali hydroxides.

B. P. Dose.—1/60 to 1/6 gr. or **1 to 10 mg.** daily. (1 mg. contains 10,000 Units of oestrogenic activity).

Oestradiolis Monobenzoas. (Oestradiol. Monobenz.). Syn.—Dihydroxyoestrin monobenzoate : Progynon B. oleosum ; Estradiol benzoate.—Oestradiol Monobenzoate is prepared by the reduction of oestrone and benzoylation of the *a*-oestradiol produced.

Characters.—Colourless crystals ; odourless. *Insoluble* in water and in aqueous solutions of alkali hydroxides ; slightly soluble in alcohol (95 p. c.).

B. P. Dose.—By intramuscular injection.—**1/60 to 1/12 gr.** or **1 to 5 mg.** daily. (1 mg. contains 10,000 Units of oestrogenic activity).

Oestradiolis Dipropionas. Syn.—Estradiol dipropionate ; Ovocylin P. ; Dihydroxyoestrin dipropionate.—Oestradiol dipropionate is **a-3 : 17-dipropionoxy-$\Delta^1 : {}^3 : {}^5$-oestratriene.**

Characters.—Colourless, crystals ; odourless. *Insoluble* in water ; slightly soluble in alcohol (90 p. c.), *soluble* in acetone and fixed oils.

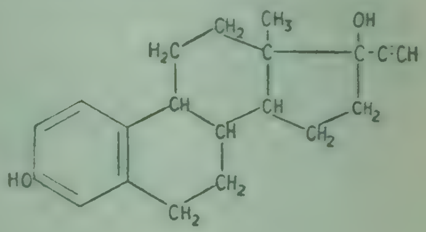
B. P. Dose.—By intramuscular injection : **1/60 to 1/12 gr.** or **1 to 5 mg.** daily.

Official Preparations

1. **Tabellae Oestroni.—B. P. Dose.—1/60 to 1/6 gr.** or **1 to 10 mg.** daily.
N. B. If the quantity in each tablet is not mentioned 1/60 gr. tablets shall be supplied.
2. **Injectio Oestradiolis Monobenzoatis.—B. P. Dose.—1/60 to 1/12 gr.** or **1 to 5 mg.** daily by intramuscular injection. N. B. When no strength is given 1/60 gr. in 15 ms. shall be dispensed.

3. **Injectio Oestradiolis Dipropionatis.—B. P. Dose.—1/60 to 1/12 gr. or 1 to 5 mg.** by intramuscular injection. N. B. When no strength is mentioned, 1/60 gr. in 15 ms. shall be dispensed.

AETHINYLOESTRADIOL. Syn.—Estinyl.—Ethinyloestradiol is 17-ethynyl-3: 17-dihydroxy-$\Delta^{1:2:3}$-oestratriene.—A fine white crystalline powder; odourless. Partially *insoluble* in water, *soluble* in acetone, in alcohol (95 p.c.), in chloroform, in solvent ether and in solutions of sodium and potassium hydroxides.



B. P. Dose.—1/3200 to 1/600 gr. or 0.02 to 0.1 mg. *daily.*

Official Preparation

1. **Tabellae Aethinyloestradiolis.—B. P. Dose.—1/3200 to 1/600 gr. or 0.02 to 0.1 mg.** daily. N. B. If the quantity to be contained in a tablet is not stated, tablets containing **0.02 mg. (1/3200 gr.) should be supplied.**

Non-official Preparations

1. **Oestradiol.** *Syn.—Dihydrotheelin ; Ovocyclin ; Dihydroxyoestrin.*—Obtained **from ovaries and from the urine of pregnancy. White crystalline substance,** sparingly soluble in water. *Dose.*—0.1 to 0.2 mg. (5000 to 10,000 i. u.) *per os* in divided doses.
2. **Oestriol.** *Syn.—Theelol ; Trihydroxyoestrin.*—Obtained from placental tissue and pregnancy urine. Almost insoluble in water. *Dose.*—0.05 to 0.5 mg. (500 **to 5000 i. u.) daily *per os* in divided doses.**
3. **Oestrone Benzoate.** *Syn.—Folliculinum Benzoicum.*—Prepared by the esterification of the phenolic hydroxy group of oestrone with benzoic acid. Almost insoluble in water. A white crystalline substance. *Dose.*—1 to 5 mg. (10,000 to 50,000 **i. b. u.) by intramuscular injection.**

(b) **Synthetic oestrogenic substances**

Whereas the natural oestrogens are complex sterol compounds, the synthetic product is a derivative of stilbene, *i. e.* 4 : 2′-dihydroxy-α : ß-diethylstilbene, generally known as diethylstilboestrol or simply stilboestrol. It is active both when used orally or parenterally.

STILBOESTROL. (Stilboestr.). Syn.—Clinestrol; Diethylstilboestrol.—Stilboestrol is 4 : 4′-dihydroxy-α : ß-diethylstilbene.

Characters.—Colourless crystals or crystalline powder ; odour, faint. Very slightly soluble in water ; readily soluble in alcohol (95 p.c.), and in solvent ether. **Soluble in aqueous solutions of alkali hydroxides.**

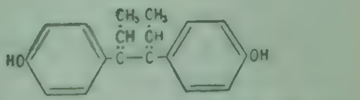
B. P. Dose.—1/120 to 1/30 gr. or 0.5 to 2 mg. daily.

Official Preparation

1. **Tabellae Stilboestrolis.** *Syn.—Tablets of Diethylstilboestrol.* **—B. P. Dose.—1/120 to 1/30 gr.** or **0.5 to 2 mg.** daily. N. B. If the quantity to be contained in a tablet **is not stated, 1/120 gr. tablet shall be supplied.**

Dienoestrol. (Dienoestr.).—Dienoestrol is 4 : 4′-dihydroxy-γσ-diphenyl-ß σ-hexadiene.

Characters.—Colourless, crystalline powder ; odourless. Almost *insoluble* in water, **readily soluble in alcohol** (95 p.c.), in acetone, in solvent ether ; **soluble in solutions of sodium hydro**xide in water.



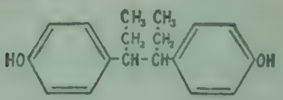
$C_{18}H_{18}O_2$ . . . . Mol. Wt. 266·3

B. P. Dose.—1/60 to 1/12 gr. or 1 to 5 mg. daily.

Official Preparation

1. Tabellae Dienoestrolis.—B. P. Dose.—1/60 to 1/12 gr. or 1 to 5 mg. daily.

Hexoestrol. (Hexoestr.) **Syn.**—Synthovo.—Hexoestrol is *meso γo*-bis-(4-hydroxyphenyl)-*n*-hexane.



$C_{18}H_{22}O_2$ . . . . . . Mol. Wt. 270·4

Characters.—Colourless crystals or crystalline powder ; odourless. Almost *insoluble* in water ; soluble in alcohol (95 p.c.), and in acetone. Slightly soluble in chloroform ; freely in solvent ether.

B. P. Dose—1/60 to 1/12 gr. or 1 to 5 mg. daily.

Official Preparation

1. **Tabellae Hexoestrolis.—B. P. Dose.—1/60 to 1/12 gr. or 1 to 5 mg. daily**

N. B. When the dose is not mentioned, 1/60 gr. tablets shall be dispensed.

Non-official Preparations

1. **Stilboestrol Dipropionate.** *Syn.—Cyrogene β.*—A colourless, crystalline substance. *Dose.*—1 to 5 mg. or 1/60 to 1/12 gr. intramuscularly. Used in preference to stiboestrol ; action slow and prolonged.

2. **Triphenylchlorethylene.**—Causes the same effect as naturally occurring oestrogenic hormones. Can be administered by mouth, by injection or as inunction. *Dose.*—Each tablet of 200 mg. (3 grs.) for oral use, and ampoules for injection contain 250 mg. (4 grs.) dissolved in 5 mils sesame oil.

Action and Uses

The therapeutic uses of oestrogens are indicated in (*a*) arrest or retardation of puberty, *e.g.* primary amenorrhoea ; (*b*) disturbances of menstruation, *e.g.* secondary amenorrhoea, menorrhagia and spasmodic dysmenorrhoea and (*c*) natural or artificial menopausal syndrome.

When subcutaneously injected into spayed rats, it produces typical oestrus, promotes the growth of uterus and vagina in the immature, causes hyperplasia of the endometrium in the mature, and cornification of the vaginal epithelium. In ovariectomised adult animals or in normal adult animal during anoestrus it induces oestrus and prevents atrophy of the accessory reproductive organs. During labour it may sensitise the uterine muscle to the expulsive action of the posterior pituitary, *i.e.* there exists a synergistic relation between oestrin and oxytocic principle of the posterior pituitary.

Since natural or artificial **menopause** is often accompanied by a variety of nervous symptoms, ovarian extract (which contains oestrin), or oestrin may be administered in those conditions depending on disordered uterine or ovarian functions, menstrual irregularity and nervous disturbances occurring during menopause, or following artificial removal of ovaries. It has also been used in hyperemesis gravidarum, sexual frigidity and in hypofunctions of the ovaries, *e.g.* amenorrhoea, functional sterility and genital hypoplasia. It has been used with success in gonorrhoeal vulvo-vaginitis of children to produce proliferation of the vaginal mucosa and desquamation of the epithelium. Oestrone is also of value in the treatment of leucorrhoea.

Ethinyloestradiol can be used orally and gives very good result in menopausal syndrome. It is many times

more powerful than oestradiol. Also used in senile vaginitis and gonorrhoeal vulvo-vaginitis. Useful in female hypogonadism and dysmenorrhoea. Usual dose by mouth is 0.05 mg. (1/1200 gr.) once to three times daily.

Oral use of oestrone will be found useful in **delayed puberty,** *i.e.* primary amenorrhoea and milder forms of menstrual irregularity characterised by deficient menstruation or oligomenorrhoea. It is however doubtful if permanent benefit follows as amenorrhoea often returns after stoppage of treatment.

Since oestrogenic hormone is responsible for the growth of the uterus and for maintaining the tone of the uterine muscle, the benzoate or propionate of oestradiol may be administered by injection in the treatment of **uterine hyperplasia, uterine inertia** and **missed abortion.** While the administration of oestrone or oestradiol benzoate helps development of the breast specially when used as inunction. A total of 2500 i.u. being rubbed into the breasts twice daily. Oestrogens have been used in *carcinoma of the prostate* and cancer of the breast. Stilboestrol often causes disappearance of the growth and alleviation of the symptoms. It has also been used in **carcinoma** of the breast and Edwards and Brown* reported favourable result following the administration of stilboestrol in doses of 0.5 to 1 mg. daily. Stilboestrol has been used with good results in **benign prostatic hypertrophy.**

Mode of administration.—Good results follow when it is given by the mouth as oestrone, by injection as oestrone or the benzoate, or in the form of suppositories.

Oestrogens may be administered through the following routes:—

1. *Oral route.*
2. *Injection,* (*a*) of oily solution, (*b*) watery solution, and (*c*) alcoholic solution.
3. *Tissue implant,* (*a*) directly in the form of tablet, or (*b*) in watery solution.
4. *Inunction.*—This is also an effective method, but causes intense local action.
5. *By vaginal or rectal insertion* in the form of pessaries or suppositories.

Comparative Activity of Oestrogens

The different oestrogens vary considerably in the intensity and duration of their action. Their activity is less marked and less prolonged with oral administration than when administered parenterally. But owing to convenience, oral administration is widely used and is effective provided it is given in adequate amounts in two or three divided doses daily. Oestriol is absorbed by the oral route more effectively and gives better results than oestrone. Oestrone however is five times more active when given by injection. Even then it is not more active than oestradiol by the mouth, and is still less active and has a less prolonged action than oestradiol benzoate by injection. Oestradiol propionate by parenteral route possesses still more prolonged action than oestradiol benzoate. Moreover,

**British Medical Journal*, 1943, 2, 659 ; Ibid. 57.

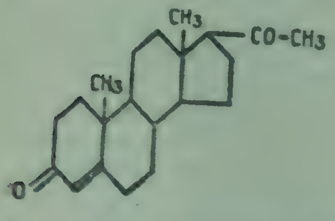
the clinical use of natural oestrogens is offset by the high cost apa from loss of potency when used orally.

Synthetic oestrogenous hormones are more potent and less e pensive than oral preparations of natural oestrins. They are tw to four times more active when given by injection but the synthe ones are more toxic. The common symptoms are gastro-intesti disturbance, nausea, vomiting, anorexia, abdominal distress an diarrhoea, headache and depression in about 20 p. c. of cases. The disappear on the stoppage of the drug. They are however rare observed in pregnant or puerperal women and in children. He oestrol is less toxic but clinically less potent. Dienoestrol is abo three times less potent and less toxic than stilboestrol.

Clinical evidence favours the use of oestrones or any of the sy thetic equivalents by mouth for low intensive therapy and oestr diol monobenzoate by injection for high intensive therapy.

The underlying principle of oestrogenic therapy is to obtain continuous therapeutic activity for a prolonged period. Therefo the drug should be administered through a route which ensures slo absorption, or in a medium which is slowly absorbed, or by using preparation which is characterised by slow absorption or slowne of action. Oestrogens, in the form of subcutaneous implant, lea to prolongation of the period of effectiveness for some months owin to the very slow absorption of the active principle from the surfa of the tablet.

II. **Corpus Luteum.**—After the discharge of the ovum the Gra afian follicle becomes transformed into the corpus luteum whic acts as a temporary organ of internal secretion. The luteal hor mone, *progesterone* or *progestin*, or an extract of the corpus luteu administered to virgin animals produces growth of the mamma glands, and is responsible for transforming the endometrium fro the proliferative phase to the pre-gravid phase essential to prepa the uterus for the reception of the fertilised ovum, and after implan tation plays an important part in the development of the placent and nutrition of the embryo and controls the development of th mammary glands. The gland enlarges during pregnancy and pro gesterone has an inhibitory effect on the uterine contraction an makes it insensitive to pituitrin. Its persistence depends upon th secretion of anterior pituitary hormone (luteinizing hormone) an when this fails towards the end of pregnancy it degenerates makin the uterus hypersensitive which reacts to an increased secretion o oxytocin and finally leads to the termination of pregnancy. On th other hand injection of this hormone causes persistence of th corpus luteum and prolongation of pregnancy beyond the norm term. Oestrin and progestin are antagonistic (675 units of oestri being neutralised by 3 units of progestin, Allen).



PROGESTERONUM. (Progesteron.) Syn.—Progestin ; Geston ; Proluton Lipo-Lutin ; Lutocyclin ; Pregnenedion —Progesterone is 3 : 20-diketo-Δ^4-preg nene. May be prepared from the cor pora lutea of the ovaries of sows o other mammals, or from stigmastero pregnanediol, or cholesterol

Characters.—Colourless crystals ; odourless. *In soluble* in water, readily soluble in alcohol, in solvent ether, chloroform, and i fixed oils.

B. P. Dose.—By intramuscular injection.—1/30 to 1/3 gr. or 2 to 20 mg. daily (1 mg. contains 1 unit).

Aethisteronum. (Aethisteron.). Syn.—Pregneninolone; Anhydrohydroxyprogesterone; Ethinyltestosterone; Proluton-C.; Progestoral.—Ethisterone is 17-ethinyl-Δ^4-androsten-17-ol-3-one.

Characters.—A white or creamy-white, minutely crystalline powder; nearly odourless; tasteless; insoluble in water; soluble in hot acetone; very sparingly soluble in chloroform and in vegetable oils.

B. P. Dose.—1/12 to 2/5 gr. or 5 to 25 mg. daily.

Official Preparations

1. **Injectio Progesteroni.** *Syn.—Proluton.*—**B. P. Dose.—1/30 to 1/3 gr. or 2 to 20 mg.** daily by intramuscular injection. N. B. When the strength is not stated, **1/12 gr. in 15 ms. shall be dispensed.**
2. **Tabellae Aethisteroni.** *Syn.—Tablets of Pregneninolone; Tablets of Ethinyltestosterone.*—**B. P. Dose.—1/12 to 2/5 gr. or 5 to 25 mg. daily. N. B. When the size of the tablet is not given, 1/12 gr. each shall be supplied.**

Action and Uses

Corpus luteum, progesterone or progestin is useful in sterility and in threatened and habitual **abortion** due to deficiency of the corpus luteum, but is contra-indicated in sterility of ovarian origin. In threatened abortion, determine if possible if the child is alive, 5 to 10 i.u. (5 to 10 mg.) daily is needed till all bleeding and pain disappear; while in habitual **abortion**, 1 to 2 mg. twice a week up to the 32nd week, or 1 mg. daily for two months beginning a month before the usual time for abortion. It has been used in functional dysmenorrhoea and pre-eclamptic toxaemia, but the results were not encouraging. Since it is probable that it suppresses menstruation it may be of value in **menorrhagia.** In functional menorrhagia 1 unit should be given daily in the premenstrual period and during the actual time of bleeding, while 500 units of the anterior pituitary factor should be injected daily then, and three times a week during two months apart from these events.* It has been used in **amenorrhoea** usually in conjunction with oestrogens. Progesterone is effective only after parenteral administration.

The Mammary Glands.—Mammary substance is related to the uterus and is useful in cases of profuse menstruation of young girls and young women, and the menorrhagia occurring at the time of menopause. It is usually combined with pituitary. *Dose.*—2 to 5 grs. (0.12 to 0.3 grm.) of the desiccated gland three times a day.

Male Sex Glands

The testicles produce an internal secretion which controls the secondary sexual characteristics. This hormone is known as *testosterone*, and is soluble in oil and obtained from the lipoid fraction of bull's testes. In the male urine *androsterone* and *dehydro-androsterone*, which are degradation products of testosterone are found. All these hormones are crystalline sterols and have been prepared synthetically from cholesterol and other sterols. They are chemically allied to female sex hormones, to vitamin D, etc.

*G. W. Corner, *Jour. Amer. Med. Assoc.* 1935.

Although the development of the secondary se characters depends upon the internal secretions of th testes, the gonads are influenced by the anterior pituitar (*see* page 444) which directly controls both spermato genesis and the internal secretory activity of the inter stitial cells.

Transplantation of the testes (Voronoff's operation) is supposed to cause rejuvenation, and has been tried i the Continent and other places. Steinach produced simi lar effects by ligating vas deferens which caused atroph of the spermatogenetic tissue and hypertrophy of th interstitial tissue.

TESTOSTERONI PROPIONAS. (Testesteron. Prop.). Syn.— Perandren.—Testosterone Propionate is 17-propionoxy-Δ^4-androsten 3-one.

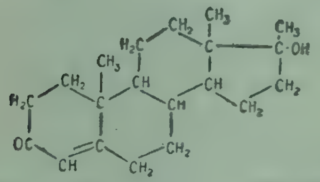
Characters.—A white or creamy-white crystalline powder ; odourless. *Solubl* in alcohol (95 p.c.), in acetone, and in fixed oils ; *Insoluble* in water.

B. P. Dose.—1/12 to 2/5 gr. or 5 to 25 mg. by intramuscular injection daily.

Official Preparation

1. **Injectio Testosteroni Propionatis.**—A sterile solution of testosterone propionate in ethyl oleate or a suitable oil. **B. P. Dose.—1/12 to 2/5 gr.** or 5 to 25 mg daily. N. B. If no strength is mentioned in the prescription, a solution containing 1/6 gr. in 15 ms. shall be dispensed.

Methyltestosteronum. (Methyltestosteron.). Syn.—Perandren Linguets; Virormone.—Methyltestosterone is 17-methyl-Δ^4-androsten-17-ol-3-one.



$C_{20}H_{30}O_2$ . . . . Mol. Wt. 302·4

Characters.—White or creamy-white crystalline powder ; odourless ; tasteless. Almost *insoluble* in water ; soluble in alcohol (95 p. c.), acetone and fixed oils.

B. P. Dose.—2/5 to 3/4 gr. or 25 to 50 mg. daily. For women :—1/12 to 1/3 gr. or 5 to 20 mg. daily.

Official Preparation

1. **Tabellae Methyltestosteroni.—B. P. Dose.—2/5 to 3/4 gr. or 25 to 50 mg.** (1/12 to 1/3 gr. or 5 to 20 mg. for women) daily. N. B. When the dose is not stated, 1/12 gr. tablets shall be supplied.

Action and Uses

The androgens (testosterone propionate and methyltestosterone) are used mainly as substitution therapy, whereas the gonadotrophins represent stimulation therapy. They have been used in sexual infantilism of moderate degree, cryptorchidism and eunuchism.

In the treatment of Frohlich's syndrome and undescended testes, testosterone should be used when both the testes are in the abdomen and do not respond to stimulation therapy with chorionic gonadotrophins. Similarly in eunuchism it is desirable to use gonadotrophins first and then use testosterone if maximal benefit does not occur. Because of its growth promoting property its use is of some value in pituitary dwarfism. The use of androgens occasionally overcomes the nervous manifestations some-

times observed in old people and which are analogous to menopausal syndrome of women.

Testosterone has been used in benign enlargement of the prostate sometimes with good result possibly by improving the muscular tone of the bladder.

Androgens may suppress menstruation in women probably due to their inhibitory action on the anterior pituitary gonadotrophic factors. Testosterone has also been used in such diverse conditions as mastitis (in the form of inunction), menorrhagia, metrorrhagia and menopausal syndrome and in carcinoma of the breast. When used in large doses or for prolonged period it may cause undesirable masculinizing effects evidenced by growth of hair on the face, deepening of voice, etc.

Testosterone may produce injury to normal testes with production of azoospermia, symptoms of heart failure in old people, oedema of the lower legs and acne vulgaris.

Being of greater activity testosterone propionate is preferred and is administered in the form of injection, daily or on alternate days in 10 to 25 mg. ($\frac{1}{6}$ to $\frac{2}{5}$ gr.) doses for males and 5 mg. ($\frac{1}{12}$ gr.) for females. Methyltestosterone is absorbed through the mucous membrane in the mouth and therefore may be used by sublingual administration, or orally for absorption from the stomach.

The Prostates.—The frequency of neurasthenic manifestation in persons suffering from prostatic disorders has led to the belief that the prostate supplied some element which normally controls the nervous system. With this idea it has been used in the treatment of neuroses that occasionally follow prostatic hypertrophy. There is no reliable evidence that the prostate furnishes an internal secretion. In fact no demonstrable defect has been noticed after removal of the glands.

Class C : Uterine Sedatives

These are remedies which inhibit uterine contraction, and are therefore of value in the treatment of threatened abortion. They should be avoided during labour as they are liable to cause uterine inertia. Few drugs, however, actually inhibit the uterine contractions, although narcotics and general anaesthetics cause some delay in labour through their effects on the central nervous system. Atropine diminishes uterine contraction by depressing the motor nerve-endings. Apart from these, certain drugs possess the reputation of being uterine sedatives, and are used in *threatened abortion*, *dysmenorrhoea*, etc. Drugs which relax plain muscles generally also reduce uterine contraction, *e.g.* nitrites and papaverine. Corpus luteum has the property of reducing the sensitiveness of the uterus to oestrin and also diminishes spontaneous movements during pregnancy. It is therefore used in cases of threatened abortion (*see* page 453).

VIBURNUM, B. P. C. Syn.—*Black Haw*.—The dried bark of *Viburnum prunifolium*. Contains (1) *Viburnin*, a glycoside. (2) A resin. (3) Valerianic, tannic and gallic acids.

Non-official Preparations

1. **Extractum Viburni Liquidum, B. P. C.**—1 in 1. *Dose.*—1 to 2 drs. or 4 to 8 mils.

2. **Elixir Viburni et Hydrastis, B. P. C.**—Ext. Viburnum Liq. 30 ms., Ext. Hydrastis liq. 5 ms. in 60 ms. with Ol. Coriander., Ol. Caraway and Glycerin. *Dose.*—30 to 60 ms. or 2 to 4 mils.

ACTION AND USES.—It has been used as a sedative in neurotic and hysterical affections but its chief use is as an uterine sedative. It is supposed to diminish or check uterine contractions occurring during pregnancy and endangering its continuance, and it is therefore used in cases of **habitual abortion**, when this does not arise from any specific cause such as syphilis or nephritis. It is used extensively in all sorts of uterine troubles, but in therapeutic doses it is of very little value.

GROUP XVI
DRUGS HAVING ANTIPYRETIC, ANALGESIC AND ANTISEPTIC PROPERTIES

Class A : Antipyretics and Analgesics
Amidopyrine, Phenazone, Phenacetin, Acetanilide

Class B : Antipyretics, Antirheumatics and Antiseptics.
Salicylic Acid, Salicylates, Acid Acetylsalicylic, Methyl Salicylas, Benzoin, Benzoic Acid, Benzoates, Cinchophen (*q.v.*).

CLASS A : Antipyretics and Analgesics

Antipyretics or Febrifuges are remedies which lower the temperature of the body in pyrexia.

Antipyretics, except when given in toxic doses, have very little effect upon the temperature in health but they act powerfully when it has been raised above normal. The maintenance of the body heat at about 98.4°F. is the result of a fine adjustment between heat production on the one hand and heat dissipation on the other, and anything which disturbs this equilibrium will cause either a rise or a fall of temperature as the case may be. Heat is lost primarily from the skin by conduction and radiation, and by evaporation of sweat ; and from the respiratory passages through warming of the inspired air, and by evaporation of water. A small amount is also lost in the excretion of urine and faeces. Excessive loss of heat is counteracted by (1) contraction of cutaneous vessels which by reducing perspiration diminishes the loss of heat ; and (2) increased combustion of tissues, whereby more heat is formed. In order to preserve the equilibrium between these factors there exists a *heat regulating centre* situated in the basal ganglia of the cerebrum and in the neighbourhood of tuber cinereum. Any lesion in its neighbourhood is followed by a rise of temperature, *e. g.* injury to corpus striatum. With the fall of temperature there is perspiration and flushing of the skin. The amount of oxygen absorbed and CO_2 given out are also diminished.

Theoretically the term *antipyretic* may be applied to various drugs which reduce febrile temperature, but it is generally restricted to a special group of drugs which lower the temperature by acting on the heat regulating

centre. The temperature is reduced by increased heat loss from dilatation of the skin vessels followed by sweating.

Most of the antipyretics are also **analgesics**, *see* **page 173.**

The temperature may be reduced by the following means :—

1. *By increasing loss of heat by acting on the thermogenic centre in the corpus striatum.*—As phenacetin, amidopyrine, acetanilide, phenazone, etc. These are true antipyretics.

2. *By dilating the cutaneous blood-vessels and thus augmenting radiation.*—As alcohol, nitrites, spiritus aetheris nitrosi, salicylates (also act by diaphoresis), warm baths.

3. *By increasing the amount of perspiration* and thus causing a loss of heat by evaporation.—(*See Diaphoretics*).

4. *By abstracting heat.*—Cold or tepid water bath, cold wet-pack, cold sponging, local irrigation with cold water, cold water compress, and evaporating lotions are agents by which we can abstract heat and thus increase heat loss.

5. *By neutralising or destroying any specific poison causing pyrexia.*—As quinine in malarial fever, sulpha-drugs and antibiotics in fever due to bacterial infection.

Caloricrescents are remedies which elevate the body temperature. The temperature may be raised either by increased heat production or diminished heat loss. Pyrexia occurs only when the change exceeds the capacity of compensation. It is a sign of disease, but may also be produced by substances which increase metabolism. Thus hyperthyroidism or administration of thyroxine is often associated with some rise of temperature.

Since certain infective organisms, *e.g.* syphilis and gonorrhoea are heat labile, *i.e.* are susceptible to high temperature and die if the temperature of the body is kept high for some hours, induction of pyrexia, *i.e.*, pyretotherapy is now recognised as an important therapeutic measure. The treatment of general paralysis of the insane by the induction of malaria is an example of **pyretotherapy.**

The following measures cause a rise of temperature :—

(*a*) *Heat puncture*, *i.e.* injury to the neighbourhood of corpus striatum. The rise of temperature is due to increased production and does not occur in glycogen-free animals.

(*b*) *Bacterial toxins* when injected, or produced in the body by infection with living bacteria. Here the rise of temperature is due to diminished heat loss. Heat production is generally increased though not always so.

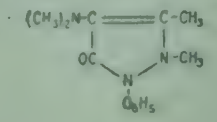
(*c*) *Certain drugs.*—Tetrahydro ß-naphthylamine causes rise of temperature of several degrees. There is increased heat production and diminished heat loss from cutaneous vaso-constriction. It is not a central effect as pyrexia occurs after the centre has been destroyed or made inactive by the previous use of antipyretics. Belladonna, caffeine, cocaine, and picrotoxin in toxic doses cause a rise of temperature.

AMIDOPYRINA

Amidopyrine. (Amidopyrin.). $C_{13}H_{17}ON_3$

Syn.—Aminopyrine ; Pyramidon.

Source.—Amidopyrine is 4-dimethylamino-1-phenyl-2:3-dimethyl-5-pyrazolone. May be prepared by methylation of the reduction product of the nitroso-derivative-of phenazone.



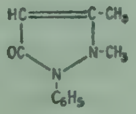
$C_{13}H_{17}ON_3$ . . . . . . Mol. Wt. 231·3

Characters.—Small colourless crystals, or a white crystalline powder. No taste or odour. *Soluble* in 18 parts of water, and in 2 parts of alcohol (90 p. c.) ; readily soluble in solvent ether.

B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

PHENAZONUM. Phenazone. (Phenazon.) $C_{11}H_{12}N_2O$. **Syn.**—Antipyrin.

Source.—It is 1-phenyl-2 : 3-dimethyl-5-pyrazolone. Obtained by the interaction of phenylhydrazine and ethyl acetoacetate, and subsequent methylation.



$C_{11}H_{12}ON_2$ . . . . . . Mol. Wt. 188·2

Characters.—Small, colourless crystals, or a white, crystalline powder ; odourless ; taste, slightly bitter, *Solubility.*—1 in 1.2 parts of water, in 1.3 of alcohol (90 p. c.), or in about 50 parts of solvent ether, and 1.3 parts of chloroform.

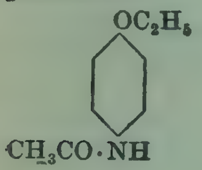
Incompatibles.—Spiritus aetheris nitrosi, tannic acid and cinchona preparations. Powdered phenazone liquefies when rubbed with butyl chloral hydrate, sodium salicylate and naphthol.

B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

Official Preparation

1. **Tabellae Phenazoni.** *Syn.—Tablets of Antipyrin.*—**B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.** N. B. If the quantity in the tablet is not stated, tablets of 5 grs. shall be supplied.

PHENACETINUM. Phenacetin. (Phenacet.). **Syn.**—Acetophenetidin.



Source.—Obtained by the acetylation of *p*-phenetidine.

Characters.—White, glistening, crystalline scales, or a fine white crystalline powder. No odour, taste, slightly bitter. *Soluble* in 1700 parts of water, in alcohol (95 p. c.), in solvent ether, and in chloroform.

B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

Official Preparations

1. **Tabellae Phenacetini.** *Syn.—Acetophenetidin Tablets.*—**B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.** N. B. If the quantity in the tablet is not stated, 5 gr. tablets shall be supplied.
2. **Tabellae Acidi Acetylsalicylici et Phenacetini.**—Contains 3½ gr. aspirin and 2½ gr. phenacetin in each. **B. P. Dose.—1 or 2 tablets.**
3. **Tabellae Codeinae Compositae.**—Contains aspirin and phenacetin, each 4 grs. and codeine phosphate 1/8 gr. in each. **B. P. Dose.—1 or 2 tablets.**

Non-official Preparations

1. **Phenazoni Salicylas, B.P.C.** *Syn.—Salipyrin ; Antipyrin Salicylate.*—White, sweetish crystals, sparingly soluble in water. *Analgesic, antirheumatic. Dose.*—5 to 20 grs. or 0.3 to 1.2 grms.
2. **Phenazoni Acetylsalicylas.** *Syn.—Antipyrin Acetylsalicylas.*—A white crystalline powder. *Analgesic, antipyretic, antiarthritic,* without injurious action on the heart. *Dose.*—8 to 15 grs. or 0.5 to 1 grm.
3. **Acetanilidum, B. P. C.** *Syn.—Phenyl-acetamide ; Antifebrin.*—Colourless, inodorous, glistening lamellar crystals ; taste, pungent. *Solubility.*—1 in 210 of cold water, 1 in 18 of boiling water, 1 in 4.2 of alcohol (90 p.c.) ; freely in chloroform and solvent ether. *Dose.*—2 to 5 grs. or 0.12 to 0.3 grm.
4. **Exalgine.** *Syn.—Methylacetanilide.*—Colourless acicular crystals. Antipyretic and analgesic. *Dose.*—1/2 to 2 grs. or 0.03 to 0.12 grm.

Pharmacology

The drugs of this group may be divided into (*a*) *aniline derivatives*, which include acetanilide and phenacetin; and (*b*) *pyrazolon derivatives*, which include amidopyrine and phenazone. Although aniline and para-aminophenol are also antipyretics, they are not used because of their toxic action. Acetanilide and phenacetin are also converted into para-aminophenol in the body but the toxic effect is less since this is formed very slowly.

Internally.—**Blood** is not affected by the ordinary doses, but its colour is changed by large doses, owing to the formation of methaemoglobin. The red blood corpuscles

are broken up, become distorted, shrunken and devoid of colouring matter, while part of methaemoglobin might escape through the kidneys, and haemoglobin and even blood may appear in the urine. This effect is due to the decomposition of the drugs and the flooding of the tissues with para-aminophenol, or the corresponding quinoline derivative. Phenazone and amidopyrine are devoid of this action as they do not form para-aminophenol derivative.

Heart and vessels.—In experimental work the heart muscle is first accelerated by ordinary doses, but in large doses the muscle is weakened and the beat becomes slow and irregular, causing collapse. This action is probably due to the sedative influence on the cardiac muscle. Acetanilide is the most depressant, next comes phenazonum ; phenacetin and amidopyrine have little or no depressant action. Collapse occurring from moderate doses is often due to idiosyncrasy. Phenazone contracts the blood-vessels by acting directly on the muscles. The blood pressure is raised at first, and is lowered subsequently from cardiac weakness.

Kidneys.—They slightly increase the flow of urine, urea and uric acid. Large doses cause haemoglobinuria. Phenazone and amidopyrine are excreted in the urine either unchanged or as oxyantipyrine in combination with glycuronic and sulphuric acids. Phenacetin appears as phenetidin compounds or as para-aminophenol. Acetanilide is excreted as para-aminophenol.

Skin.—Papular, erythematous and urticarial rashes are observed at times. They may produce a slight **diaphoresis** in health, but a copious one in pyrexia.

Temperature.—All these drugs are powerful **antipyretics.** They have little effect in reducing the temperature in health except when given in toxic doses so as to produce collapse, but they reduce temperature when it is high, as in fever, due to the fact that in fever the heat regulating centre is in an abnormal state and is more susceptible to these drugs. As a rule the temperature begins to fall within two hours and generally comes down to normal or even to subnormal and is accompanied by profuse sweating preceded by vaso-dilatation which is confined to the skin and is a central effect. This was at one time believed to be the cause of the fall, but the temperature falls even when the perspiration is checked by the previous use of atropine. The antipyretic effect is the result of direct action on the heat regulating mechanism causing an increased heat dissipation from dilatation of the cutaneous vessels. In fact the perspiration is preceded by a feeling of external heat and flushing of the face. Amidopyrine is a more powerful antipyretic and analgesic than others.

Nervous system.—All these drugs are powerful

analgesics, and though not strongly hypnotic, yet taken at bedtime they favour the onset and maintenance of normal sleep. The pain sensation is abolished and they do this without any appreciable effect on the mental activity. It has been suggested that the analgesia is the result of an action on synapses in the pain conveying tract in the thalamus adjacent to the heat centre. Most of the antipyretics and notably acetanilide and phenazone increase motor excitability of the cord and cause convulsions, specially in frogs. How they are produced in mammals is not definitely known, possibly they are cerebral. When large doses are introduced into the blood directly the convulsions resemble those of strychnine inasmuch as they are spinal and are produced after separation of the cord from the brain. It has been suggested that they may be due to asphyxia and not to any direct effect on the brain. The peripheral nerves and the nerve-endings are not affected even in poisoning.

Clearance.—These drugs are rapidly absorbed and eliminated. Acetanilide and phenacetin are mainly converted into para-aminophenol. They are excreted in the urine and disappear from the body within 24 hours.

Toxic action.—Large doses cause great prostration, sometimes vomiting, weak, irregular pulse, slow respiration and sweating. In toxic doses these symptoms are aggravated leading to profuse sweating, cyanosis, collapse and death. Sometimes a rash appears on the skin. Poisoning may occur from phenazone and acetanilide.

Treatment.—Warmth to the surface, stimulants, strychnine and atropine hypodermically, and oxygen inhalation.

Therapeutics

Internally.—As **antipyretics** all these drugs are used to reduce fever heat, but phenacetin, being the safest, is prescribed more frequently. They take about two hours to bring down the temperature, but phenazone and acetanilide do it more rapidly. To maintain the reduced temperature they require to be repeated every 4 hours, and this sometimes leads to dangerous symptoms on account of their depressing influence on the heart. They cannot control the duration of fever, for as soon as the effects are over the fever rushes up again. Hence many physicians are averse to using them as antipyretics as a routine treatment, but they are very useful agents in cases where the temperature is so high as to endanger life, where the high temperature is the chief cause of distress, and where reduction of temperature and increased comfort are not counterbalanced by their masking the true condition of the disease. A more serious objection to the use of these drugs is that the course of the disease may be obscured as the natural daily variation of temperature which often guide the physician regarding the course of the disease

and its severity is masked making diagnosis and prognosis more difficult. In hyperpyrexia they cannot be relied upon. Both phenazone and phenacetin have been given in every form of febrile condition with a high temperature but with unsatisfactory results. In fact one should not use drugs which act on the heat regulating mechanism, but should rely, for the reduction of temperature, upon those means which promote the dissipation of heat without influencing the centre.

A very important use of these drugs depends upon their valuable property of relieving certain types of pain chiefly of neuralgic character. As **analgesics** therefore these drugs are largely used to relieve pain. For reasons already stated, phenacetin will have the preference. There is hardly any pain which cannot be alleviated by phenazone. Five to 10 grs. given hourly for 3 or 4 doses give relief in almost every form of headache and migraine. Phenacetin does it equally well in 5 gr. doses. Moreover, the pains of ataxy, sciatica, angina, internal aneurism, dysmenorrhoea are soon cut short by these drugs. These drugs are often used in preference to morphine because of its liability to produce a habit. They are of little value in pains of spasmodic nature, for instance, renal colic, when morphine is the drug of choice.

As a nervine sedative, phenazone is occasionally used in epilepsy, chorea, nocturnal emissions, laryngismus stridulus, asthma, sea-sickness, enuresis, etc. Antipyrin has been used in **whooping cough,** and is often combined with belladonna when it gives relief by not only lessening the severity of the attacks but by actually shortening the course of the disease.

Untoward effects.—Sometimes evidence of toxic manifestations are noticed following the use of antipyrin. These are chiefly due to idiosyncrasy. They are (1) urticarial rash, erythematous or bullous eruptions with or without oedema of the skin, mucous membrane and glottis; (2) gastric intolerance, avoided by combining with alkalies; (3) profuse perspiration, subnormal temperature and a tendency to collapse, specially in tubercular and cachectic patients; (4) cyanosis, fall of blood pressure and intermittent pulse; (5) albuminuria, specially after long continued use.

Amidopyrine sometimes caused agranulocytosis, a condition characterised by severe leucopenia, ulcerative angina, prostration followed by death. Other drugs, notably gold, sulphonamides, thiouracil and organic arsenic compounds have also been found to produce this effect.

Prescribing hints.—All these drugs may be given in powders, cachets or capsules. Phenazone being soluble in water can be given in peppermint water which disguises its taste, while the others can be suspended by compound tragacanth powder. Sometimes they may be given with advantage in brandy or whisky. Acetanilide is not so much used nowadays because of its liability to toxic effects. As a rule phenazone and amidopyrine do not produce any side-effects although the latter drug has been known to produce agranulocytosis, which has reduced the popularity of this drug. The student should

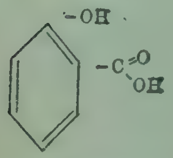
remember that antipyrin when triturated with calomel forms a toxic compound, and with chloral and sodium salicylate forms oily liquids. The solubility of the salts of quinine and caffeine is increased by the addition of antipyrin. On account of a long list of incompatibles phenazone is better given alone.

Class B : Antirheumatics and Antiseptics

ACIDUM SALICYLICUM

(Acid. Salicyl.).

Source.—Salicylic Acid may be obtained by the interaction of sodium phenoxide and carbon dioxide. Contains not less than 99.5 p.c. of $C_7H_6O_3$.



Characters.—Colourless crystals, or a light feathery crystalline powder, almost odourless ; taste, sweetish and acrid. *Solubility.*—1 in 500 parts of water, and in 3.5 parts of alcohol (90 p.c.), readily in solvent ether, and in chloroform ; soluble in solutions of ammonium acetate, of sodium phosphate, and potassium and sodium citrate.

Incompatibles.—Iron salts, quinine sulphate, sp. aether. nitros. and sp. ammon. aromat.

Official Preparation

1. **Unguentum Acidi Salicylici.**—Salicylic acid 2 p. c.

SODII SALICYLAS. (Sod. Salicyl.). $NaC_7H_5O_3$.—Sodium Salicylate is obtained by the interaction of salicylic acid and sodium carbonate. It contains not less than 99.5 p.c. of pure sodium salicylate.

Characters.—Colourless, small crystals or crystalline flakes, or a white powder ; odourless, or with a faint characteristic odour ; taste, sweetish, saline, unpleasant. *Solubility.*—1 in 1 of water, 1 in 6 of alcohol (90 p.c.).

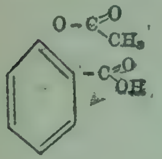
Incompatibles.—Acids, antipyrin, quinine and iron salts.

B. P. Dose.—10 to 30 grs. or 0.6 to 2 grms.

Official Preparation

1. **Tabellae Sodii Salicylatis.—B. P. Dose.—10 to 30 grs. or 0.6 to 2 grms.** N. B. If the quantity to be contained in a tablet is not stated, 5 gr. tablets shall be supplied.

ACIDUM ACETYLSALICYLICUM. (Acid. Acetylsalicyl.). Syn. —Aspirin.—Acetylsalicylic Acid is obtained by the action of acetic anhydride or of acetyl chloride on salicylic acid. Contains not less than 99.5 p.c. of $C_9H_8O_4$.



Characters.—Small, colourless, acicular crystals, or a white crystalline powder. Odourless ; taste, slightly acid. Stable in dry air, but in contact with moisture gradually hydrolyses into acetic and salicylic acids. *Soluble* in 300 parts of water, in 5 parts of alcohol (90 p.c.), and strong solution of ammonium acetate.

B. P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Official Preparations

1. **Tabellae Acidi Acetylsalicylici.** *Syn.—Tablets of Aspirin.*—**B. P. Dose.**—5 to 15 grs. or 0.3 to 1 grm. N. B. If the quantity in a tablet is not stated, 5 gr. tablets shall be supplied.
2. **Tabellae Acidi Acetylsalicylici cum Ipecacuanha et Opio.**—See page 175.
3. **Tabellae Acidi Acetylsalicylici et Phenacetini.** *Syn.—Aspirin and Phenacetin Tablets.*—3½ gr. aspirin and 2½ gr. phenacetin in each. **B. P. Dose.**—1 or 2 tablets.
4. **Tabellae Codeinae Compositae.** *Syn.—Tablets of Aspirin, Phenacetin and Codeine.*—Aspirin and phenacetin, each 4 grs., codeine phosphate 1/8 gr. in each. **B. P. Dose.—1 or 2 tablets.**

Non-official Preparations and Derivatives of Salicylic Acid

1. **Salicin, B. P. C.**—It is a glucoside obtained from the bark of various species of *Salix*, and of *Populus*. Colourless crystals or white crystalline powder. *Dose.*—5 to 15 grs. or 0.3 to 1 grm.
2. **Calcii Acetylsalicylas.** *Syn.—Tylcalsin.*—White amorphous, non-hygroscopic powder. Soluble 1 in 6 of water but dissociates in solution. *Dose.*—5 to 15

grs. or 0.3 to 1 grm. *Antirheumatic* and *influenza specific.* Combines the good effects of sodium salicylate and aspirin.

[illegible] Collodium Acidi Salicylici, B. P. C. *Syn.—Corn Paint.*—Salicylic Acid 12, Extract of Indian Hemp 2, Acetone 30, Acetone Collodion to 100. A painless solvent for hard and soft corns.

[illegible] Conspersus Acidi Salicylici Co., B. P. C. *Syn.—Pulvis pro Pedibus.*—Acid salicylic 3, boric acid powder 10, sterilised purified talc 87.*

[illegible] Conspersus Zinci Oxidi et Acidi Salicylici, B. P. C. *Syn.—Zinc Oxide and Salicylic Acid Dusting Powder.*—Zinc oxide 20, salicylic acid in powder 5, starch in powder 75.

PHARMACOLOGY

Externally.—Salicylic acid is an antiseptic. A 2 p.c. solution of the acid kills bacteria and checks fermentation, but its salts have no antiseptic properties. It is a powerful local anhidrotic. It has special action on the epithelium and in dilute form the acid acts as a keratoplastic agent, and aids regeneration of new epithelium. In a concentrated form it acts peculiarly on the epidermis specially the corneous layer, and the horny cells are softened, gradually loosened and separated without much inflammatory reaction.

Internally. **Alimentary canal.**—Salicylic acid is an irritant to the stomach and when taken undiluted causes pain, nausea and vomiting. Vomiting in cases of poisoning is a central effect. Sodium salicylate and salicin are less irritant. Salicin is a bitter stomachic and is transmitted unchanged into the intestine, where it is broken up probably by the help of the pancreatic juice into saligenin and glucose, and saligenin again into salicyluric, salicylous and salicylic acids. Acid acetylsalicylic passes through the stomach unchanged and therefore does not act as an irritant here, but is decomposed partly into salicylic acid in the gut and is absorbed as sodium acetylsalicylate. In some persons aspirin is liable to cause indigestion, heart-burn and occasionally epigastric pain. Multiple gastric submucous haemorrhages and even haematemesis may occur.

Liver.—The salicylates are efficient biliary antiseptics. They increase the secretion of bile, possibly from some specific action on the liver cells. The bile is rendered thin and watery. There is however a total increase in the solids of the bile.

Blood.—Salicylic acid enters the blood as sodium salicylate, in which form it is found in the blood. It is possible that sodium salicylate is converted again into salicylic acid by carbonic acid in the inflamed joints. A portion of the salicylic acid of the salicylate unites with glycine either in the blood or tissues to form salicyluric acid. Effective concentration in the blood is 35 mg. per 100 mil. The amount of salicylate required to maintain this concentration varies from 7.2 to 17.4 grm. When the concentration rises above 40 mg. per 100 mil toxic symptoms appear.

Heart and blood-vessels.—In therapeutic doses salicylic acid, sodium salicylate and salicin have very little effect on

*Conspersus or dusting powder.

circulation except in susceptible persons when it may be accelerated. Large doses make the heart slow and weak, the muscles get relaxed and dilated causing a fall of pressure from depression of the centre. Physiologically pure artificial salt is not depressant.

Antipyretic and analgesic action.—They are both analgesics and antipyretics, but this action is found in large degree with acetylsalicylic acid. The skin vessels dilate producing a sensation of heat followed by perspiration like drugs of the antipyretic group by acting on the thermogenetic centre. In healthy individuals this is compensated by increased heat production, so that the normal temperature is not easily affected. A single dose of 20 to 30 grs. of sodium salicylate may bring down the temperature from 105°F. to 101°F. in 2 or 3 hours. Aspirin however will produce free perspiration and reduction of temperature in 10 gr. doses.

Skin.—Salicylic acid, aspirin and sodium salicylate increase perspiration due to (1) dilatation of the cutaneous vessels, and (2) according to Cushny to increased activity of the sweat centre. Dilatation of the skin vessels may cause some skin rashes to appear.

Metabolism.—Salicylates diminish the renal threshold to uric acid which is increased up to 100 p.c. even in purine free diet. Due to increase of fixed acid and lowering of reserve alkalies combined with defective excretion due to damaged kidneys it causes **non-gaseous acidosis.** Both salicylates and aspirin **delay clotting** and lower the prothrombin level of the blood similar to decoumarol but they are less potent. Toxic doses may favour haemorrhage. Opinions differ whether therapeutic doses induce haemorrhage. Administration of menaphthone or vitamine K will counteract this effect.

Kidneys.—Secretion of urine is increased to some extent possibly due to its direct action on the renal cells. Salicylic acid is excreted in the urine as salicyluric acid and sodium salicylate. It sometimes causes nephritis with bloody and albuminous urine. Through stimulation of nuclein metabolism and increased leucocytes it raises the uric acid in the blood and increases the excretion of urea and uric acid, and gives sometimes to the urine greenish colour due to the presence of pyrocatechin. It renders the urine **antiseptic** and **increases its acidity.** The urine of patients taking salicylic acid gives a purple colour solution with ferric chloride.

Uterus.—Some think that salicylic acid is an **emmenagogue** and may cause abortion, but there is no sufficient evidence to confirm this statement.

Elimination.—Salicylates are excreted to some extent in all the secretions, chiefly by the urine, and to a less ex-

tent by the sweat, saliva, bile, sputum and faeces. The excretion begins within 15 minutes and is practically completed in 6 to 8 hours. About 50 p. c. is excreted in the first 24 hours and a total of 80 p.c. of the doses administered is excreted within 48 hours in normal individuals. The rapid excretion explains the necessity of large and repeated doses.

Aspirin is about one and one-half times more toxic than sodium salicylate. Even small doses (5 to 10 grs.) occasionally produce alarming symptoms. It is however a stronger analgesic and antipyretic due to the undecomposed acetyl compound entering the nerve cells more rapidly.

Toxic action.—Mild toxic symptoms may appear when cases of rheumatic fever are treated with large doses of salicylates. The symptoms resemble cinchonism, buzzing in the ears, disturbed hearing and vision, headache, vertigo, mental confusion from disturbance of circulation of the brain are the early symptoms. When these appear further use of the drug should be stopped. If however it is pushed further, nausea, vomiting, deafness, delirium, flushed face, free perspiration, rapid pulse, deep and accelerated respiration and air hunger may be present. More serious toxic effect is haemorrhage due to fall of prothrombin in the blood.

All the symptoms of salicylism have been attributed to a marked disturbance in acid-base equilibrium and formation of **non-gaseous acidosis** and does not occur when the drug is used with sufficient alkali. This acidosis is the result of increased production of acids combined with defective excretion due to a damaged kidney.

Therapeutics

Externally.—Salicylic acid is occasionally used in surgical practice in the form of a lotion, ointment, lint, cotton, etc. In lupus, corns and tylosis, collodium acidi salicylici is a useful application. An ointment containing 30 grs. each of phenol and salicylic acid in 1 oz. cures ringworm. Being non-volatile it is not an effective antiseptic for deep suppurating wounds. Salicylic acid and talc powder checks fetid perspiration of the feet and armpits. A 1 to 4 p.c. solution or the ointment often relieves the itching of eczema, intertrigo and urticaria. Salicylate of soda is also used by ionisation in case of fibrositis.

Internally.—As an *antirheumatic*, the salicylates are considered specifics for **acute rheumatism.** They reduce the temperature, lessen the swelling, and relieve the pain, if 20 to 30 grains are given every 2 hours, until about six doses are taken, and then at longer intervals. This specific action is produced only when the body is saturated with the salicylate, and the action remains as long as this saturation is maintained. Once however the urgent symptoms are relieved the dose may be reduced, but it has to be used for a prolonged period. If the dose is reduced too much the symptoms return again. Even after an apparent cure the treatment should be continued for one or two weeks. The

liability to cardiac complications is minimised by salicylate treatment, although some authorities aver that the tendency to both endocarditis and pericarditis is greatly increased by the use of salicylates in acute rheumatic fever. Experience has shown that the cardiac complications are less if the patient is kept in bed for a long time, which also minimises any risk of permanent damage to the heart. Sodium salicylate may also be used as intravenous injection. The intravenous route is safe and painless and is best suited for cases where the drug is not well tolerated when given by the mouth or causes no improvement. The following solution may be used, *viz.*—Sodium salicylate (pure) 120 grs. or 8 grms. in freshly sterilised distilled water $1\frac{2}{3}$ ozs. or 50 mils. Of this 2 mils are injected once or twice a day. If necessary 30 grs. or 2 grms. of caffeine sodium benzoate may be added to the above solution. In the hyperpyrexia of rheumatism salicylates are of no use. In chronic rheumatoid arthritis and gonorrhoeal arthritis, opinions differ as to their utility. As an antirheumatic aspirin is inferior to the salicylates, but is frequently of some value in chronic cases, since it is usually better borne and is probably more slowly eliminated. Because the salicylates increase excretion of uric acid they are of value in **gout** specially when combined with colchicum.

Sodium salicylate 3 grs. given hourly gives good results in quinsy. Aspirin is more freely used in the form of tablets for colds, sore-throat, headache and influenza.

Intravenous injection of sodium salicylate has been used with success in **psoriasis** (10 mils of a 20 p.c. solution) given three times a week for 4 to 5 weeks, and in encephalitis lethargica.

As a **sclerosing agent** sodium salicylate has been used in the injection treatment of **varicose veins.** For this 3 mils of a 20 p.c. solution is injected into the vein, the varices being first made empty of blood. One injection generally suffices, but if necessary this is followed, a week later, by another injection of 30 p. c. solution. If combined with 10 p. c. sodium chloride these injections are practically painless. Great care should be taken in giving these injections since any leakage into the surrounding tissue may cause sloughing.

As a *hepatic stimulant*, all these drugs may be given in torpidity of the liver and catarrhal jaundice, but sodium salicylate is the most effective. Sodium salicylate and aspirin are both useful in the treatment of hepatic colic, and are given with benefit as solvents of gall-stones.

As an *analgesic*, sodium salicylate may be given in neuralgias and lumbago, and is considered to be an effective remedy for sciatica. In chronic sciatica it gives the

est result when combined with iodide. As an analgesic spirin is superior to sodium salicylate and resembles the rugs of the phenacetin group, and is used to relieve pain f diverse nature in preference to sodium salicylate. As a *edative* both sodium salicylate and aspirin have been used n chorea in doses of 10 grs. three times daily.

Salicylate sometimes helps absorption of effused fluid nd has been used in the treatment of **pleurisy.** How it elps this is not understood and the little diuresis which ollows its use will not explain the mechanism of its action.

Sodium salicylate and aspirin have been found to re-luce the quantity of sugar in the urine in diabetes.

Prescribing hints.—Sodium salicylate is best given in solution. f mixed with ammonia the mixture gradually turns from pale-yellow o brown on exposure to air. When given with quinine or citric cid, precipitation occurs. Sodium salicylate in an acid and aspirin n an alkaline medium will precipitate salicylic acid and may cause iscomfort, damage of the mucosa and gastric haemorrhage. Aspirin s best administered in cachets, tablets or in powders. Alcoholic olutions decompose it to salicylic acid and acetic acid on standing. t may be given in milk to children.

On account of the rapid elimination the quantity required hould be divided into several doses and given every three or four ours. When treating cases of rheumatism with large doses, odium salicylate should be freely diluted and combined with bi-arbonate of soda to avoid irritation of the stomach and acidosis. t also helps excretion, therefore tends to diminish its action. To revent hypoprothrombinaemia it should be used with vitamin K. Salicin is not freely soluble in water but the addition of glycerin ncreases its solubility.

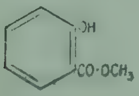
Sodium Gentisate.—It has been suggested that rheu-matic infection has some relationship with *hyaluronic acid* which is a mucopolysaccharide and possesses the pro-perty of binding water and forming a jelly-like matrix and serves as a lubricant and shock absorber in joints. This acid is hydrolysed by enzyme *hyaluronidase* found in a arge variety of biological fluids as also within some micro-organisms (several strains of *Str. haemolyticus*). It is believed that in rheumatism the action of the enzyme hyaluronidase is increased which is responsible for some of the characteristic manifestations of the disease parti-cularly those of the joints. On the supposition that the specific action of the salicylate may be due to gentisic acid (gentisic acid contains only one extra OH group) to which salicylic acid is converted and which is a powerful inhibitor of the enzyme hyaluronidase, sodium gentisate has been used in the treatment of rheumatism in doses of 10 grm. daily without any toxic effect and with as satisfactory result as with sodium salicylate. It is, however, too early to pass any judgement on this new conception of the cause of rheumatic fever as also on the value of sodium gentisate.

Methylis Salicylas. (Methyl. Salicyl.). $C_8H_8O_3$. **Syn.**—Artificial Oil of Wintergreen.—Methyl Salicylate may be prepared by the

esterification of salicylic acid with methyl alcohol. Contains not less than 98 p.c. of pure methylsalicylate.

Characters.—A colourless, or pale yellow liquid. Characteristic, aromatic odour; taste, sweet, warm, aromatic. Slightly *soluble* in water, freely in alcohol (90 p. c.).

Enters into.—Cataplasma Kaolini.



$C_8H_8O_3$ . . . . . . Mol. Wt. 152·1

NON-OFFICIAL PREPARATIONS

1. **Linimentum Methylis Salicylatis, B. P. C.**—Methyl salicylate 25, arachis, cottonseed or rape oil to 100. As a paint over *rheumatic joints* and *neuralgic areas*, the part being covered with oil silk.

2. **Ung. Methylis Salicylatis Co., B. P. C.** *Syn.—Analgesic Balsam.*—Methyl salicylate 50, menthol 10, eucalyptol and oil of cajuput (by wt.) each 2.5, white beeswax 20, lanoline 15. In *sciatica, lumbago* and *rheumatism.*

3. **Linimentum Methylis Salicylatis et Eucalypti, B. P. C.**—Menthol 5, oil of eucalyptus 10, rectified oil of camphor 25, methyl salicylate to 100.

ACTION AND USES.—The action and uses of methyl salicylate are much the same as those of the salicylates. As it is absorbed by the unbroken skin it is used externally either as liniment or ointment. It may also be used internally in capsules.

BENZOINUM

Benzoin. (Benzoin.)

Syn.—Gum Benjamin; Sumatra Benzoin. *Loban*, Beng.—A balsamic resin obtained from the incised stem of *Styrax Benzoin* and of *Styrax Paralleloneurus*, known in commerce as Sumatra benzoin, or from the incised stem of *Styrax tonkinensis*, known in commerce as Siam benzoin.

Characters.—In hard, brittle masses consisting of whitish or reddish tears embedded in a greyish-brown or reddish-brown translucent matrix. Odour, agreeable; taste, slightly acrid. When heated it melts and evolves whitish fumes with an irritating odour.

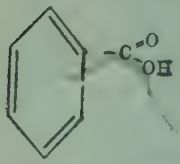
Composition.—(1) *Benzoic acid* 18 p. c. (2) *Cinnamic acid* 20 p. c. (3) *Volatile Oil.* (4) *Resins.*

Enters into.—Adeps Benzoinatus (Siam benzoin).

OFFICIAL PREPARATION

1. **Tinctura Benzoini Composita.** *Syn.—Friar's Balsam.*

Acidum Benzoicum. (Acid. Benz.). $C_7H_6O_2$—Benzoic Acid is obtained from benzoin, or prepared synthetically.



Characters.—In light feathery, colourless and odourless crystals. Melts and sublimes on heating. *Solubility.*—1 in 450 parts of water, 1 in 3 of alcohol (90 p. c.), freely in chloroform and solvent ether.

Incompatibles.—Ferric salts and mercuric chloride.

Enters into.—Tinct. Opii Camphorata.

Sodii Benzoas. (Sod. Benz.). $NaC_7H_5O_2$—Sodium Benzoate is prepared by neutralising benzoic acid with sodium carbonate. A white, amorphous, granular or crystalline powder; odourless, with a faint benzoin odour. Taste, unpleasant, sweetish and saline. *Solubility.*—1 in 2 parts of water, slightly in alcohol (90 p. c.).

B. P. Dose.—5 to 30 grs. or 0.3 to 2 grms.

NON-OFFICIAL PREPARATIONS

1. **Cryogenine.** *Syn.—Meta-benzaminosemicarbazide.*—A crystalline body sparingly soluble in water, used in *pyrexia of phthisis* and *enteric fever.* Has no depressing action. *Dose.*—3 to 24 grs. or 0.2 to 1.5 grms.

2. **Vapor Mentholis et Benzoini, B. P. C.**—Menthol 8 gr., benzoin (Sumatra) crushed 45 gr., prepared storax 30 gr., alcohol (95 p.c.) to 1 oz.

PHARMACOLOGY

Externally.—Both benzoin and benzoic acid are antiseptics. A concentrated solution is a local stimulant and irritant.

Internally. **Gastro-intestinal tract.**—The salts are less irritant and are therefore used in preference to the acid. In small doses they have little effect on the stomach and intestine, but in large doses irritate them. The acid is an intestinal disinfectant.

Respiratory tract.—Both the gum and the acid cause sneezing when inhaled. The vapour directly stimulates the bronchial secretion which is also stimulated during excretion when the benzoate is given by the mouth. Hence benzoin and sodium benzoate are **expectorants.** They also disinfect the secretion.

Urinary tract.—Benzoic acid and its salts are largely excreted with the urine, partly unchanged, but chiefly as hippuric acid. The appearance of hippuric acid in the urine is due to the combination of benzoic acid with glycine in the body. Hippuric acid so formed stimulates the activity of the renal cells and renders the alkaline urine acid. Hence benzoic acid and benzoates are diuretics and acidifiers of alkaline urine. Over the mucous membrane of the urinary tract they have a disinfecting influence.

Temperature.—Benzoic acid and benzoates are antipyretics, sometimes acting more powerfully than salicylic acid, but how they act is not known.

Metabolism.—They increase metabolism and there is excess of nitrogenous constituents of urine, and the body weight falls. Benzoic acid reduces the excretion of uric acid.

Elimination.—Chiefly with the urine, and partly with the sweat, saliva and bronchial secretion, which are stimulated to a slight extent.

THERAPEUTICS

Externally.—A piece of lint soaked in Friar's balsam may be used to stop bleeding from, and promote the healing of, fresh wounds. Locally applied, it relieves the pruritus of urticaria, and in solution (5 p.c. of the compound tincture with 5 p.c. of glycerin in water) it is a soothing stimulant application for the skin after the cure of acne.

Internally. **Lungs.**—Both benzoin and benzoates are largely employed, either by the mouth or as an inhalation, in chronic bronchitis and phthisis, particularly if the expectoration is foul and scanty. The vapour of the tincture cuts short attacks of catarrh and influenza and is useful in inflamed tonsils.

Urinary tracts.—As an *acidifier* of alkaline decomposing urine in cystitis or pyelitis, and in phosphatic calculi, benzoates have been replaced by acid sodium phosphate which is more powerful in acidifying alkaline urine, and by sulphonamides which are better and more powerful urinary antiseptics.

Rheumatism and gout.—Benzoate of soda may be given in acute rheumatism when sodium salicylate cannot be borne or fails to do good. In gout it is occasionally used with the idea that it converts uric acid into hippuric acid and thus helps its elimination.

Prescribing hints.—With acids the benzoates are decomposed into insoluble benzoic acid, and with ferric salts form insoluble flesh coloured ferric benzoate. They are also incompatible with lead, silver and mercury. Most alkaloids form insoluble benzoates. The vapour may be inhaled through an inhaler.

GROUP XVII
CHEMOTHERAPEUTIC AGENTS

Pharmacology deals with the physiological action of drugs and forms only a basis for the relief of symptoms rather than the cure of disease. Drugs like digitalis, adrenaline, pituitrin, etc., do not remove the underlying causes of the disease, although by relieving some urgent symptoms they remove the cause of distress and often act as curative agents. It is, however, in cases of diseases caused by micro-organisms or other parasites, that drugs may act purely as curative agents, and this specific treatment of infection is known as *chemotherapy*, *e. g.* treatment of syphilis by organic arsenic preparations, of amoebic dysentery by emetine, and of malaria by quinine and other antimalarial drugs. The term was originally used by Ehrlich to mean parasiticidal treatment of infections by chemical agents. Since certain dyes are able to stain specifically certain cellular elements, a search was made to find substances which would unite with and destroy the parasitic agents of the disease without injuring the cells of the body, *i.e.* possess a maximum parasitotropic effect and a minimum organotropic property. But substances which are toxic to the parasite are also to a certain degree toxic to the body tissues. The object of chemotherapy, therefore, is to find substances which the tissues will stand in large doses, but will be fatal to the infecting organism in small doses, *i.e.* will have a favourable chemotherapeutic index, which is

$$\frac{\text{maximum tolerated dose}}{\text{minimum curative dose}}$$

The greater the index, the greater will be its value.

With the growth of our knowledge regarding the

causation of the different infections and the progress of synthetic chemistry, newer remedies are being daily introduced which give promising results, so that remedies which were classed as specifics cease to be so in the presence of the many newer drugs which approach more towards specific action. In fact the word specific is used to mean that a particular preparation is more toxic to one particular parasite than on another or nearly related one.

Evidence is accumulating in favour of the view that drugs which are supposed to have a specific action, in a majority of instances, act by what is known as "substrate competition" (see page 48). Drugs having chemical structure almost similar to the essential metabolites of some of the organisms, offer competition with the same for a position in the enzyme system. As a result of this reaction, the organisms are deprived of their essential metabolites and therefore fail to grow and reproduce, are reduced in number and weakened, and are ultimately destroyed by phagocytes and other anti-bodies present in the host particularly by the cells of the reticulo-endothelial system. In fact Maher (1944) came to the conclusion that this system was vital to the manifestation of sulphonamide chemotherapy.

Many drugs act as specifics within the body of the host while possessing little or no such effect outside the body. In fact it has been shown (*see* page 52) that the co-operation of the host is an important factor in the production of the specific action of a drug. It has therefore been suggested that the reticulo-endothelial system is responsible for the formation of the natural defensive mechanism which is an important factor in the causation of cures in different infections, and that dysfunction of this system by 'blockade' or splenectomy experiments reduces or even completely abolishes the therapeutic value of a drug.

The exact manner in which the system responds to the stimulus of the specific drug depends upon the nature of the infecting organism. While some parasites are rapidly destroyed by phagocytes, others require to be disposed of by the destructive action of the lytic antibodies. In the first instance the response is evidenced by mobilisation and functional activation of the phagocytic cells of the system, while in the case of the other there is increased antibody production. When both these methods are of little use, the system utilises other methods, one being the elaboration of a powerful parasiticidal substance from the drug used. The modern conception of the specific action of a drug is that it stimulates the natural processes of the body in the cure of disease by bringing about such changes, directly or indirectly, either on the parasite or its environment as would be conducive to the success of the natural processes at work.

The different ways in which this system helps drugs in acting as specifics are as follows :—

1. By acting as a store-house for the drug and elaborating it

slowly as required, thus preventing its rapid escape from the body and ensuring continuous supply.

2. By carrying the medicament to the neighbourhood of the lesion where it is most needed.

3. By possibly forming new compounds with greater parasiticidal properties.

4. It is possible that the drug stimulates the system in the production of more pronounced and effective phagocytic action and formation of antibodies.

The reticulo-endothelial system is composed of a special group of cells of mesenchymal origin and of the macrophage or large mononuclear type possessing the property of phagocytosis and intracellular digestion. These cells are found in the liver, spleen, bone-marrow and lymphatic glands, and to a greater or lesser degree in other parts of the body. The cells composing this system are of six types of which *monocytes* and *histiocytes* or *clasmatocytes* possess powerful phagocytic properties. Both in health and disease this system performs diverse important functions of which phagocytosis is perhaps the chief and most important one, and it is possible that most of its other functions more or less depend upon this property.

The different functions of the reticulo-endothelial system may be classified as follows :—

1. *Formation of bile pigment.*—The red blood cells are broken up for the formation of bile pigment by all tissues in which reticulo-endothelial cells are present including the Kupffer's cells in the liver, but not by the glandular cells of that organ.

2. *Destruction and regeneration of red cells.*—It has been shown that the cells of this system take up for purposes of destruction those red cells whose alloted span of life is over, or those that have become damaged as a result of some inflammatory processes, toxins or parasitic invasion. Along with destruction there is also regeneration, and these two processes go hand in hand so that the red cell count is maintained at a constant level. In fact this system supplies the stimulus for regeneration of red cells, and in the absence of such stimulus the bone-marrow fails to manufacture sufficient number of red cells to maintain the equilibrium.

3. *Iron metabolism.*—Closely related to the regeneration of the red cells is the property of this system to utilise the iron from the degenerated red cells for the formation of fresh red cells. This metal (haemosiderin) is stored in the liver and spleen by the reticulo-endothelial cells which is metabolised in the synthesis for the manufacture of haemoglobin.

4. *Cholesterol metabolism.*—Experimental evidence goes to show that storage of cholesterol is another important function of this system.

5. *Phagocytosis of bacteria and particulate substances.*—Experimental observations have shown that this system has the property of engulfing different bacteria and other organisms, *e.g.* protozoa, and carry them to internal organs, like the spleen and liver, for purposes of destruction. In many infectious diseases these cells have been found to be actually loaded with different organisms in infected tissues. There is enough evidence to show that these cells readily ingest substances like Indian ink particles, vital dyes, carbon, colloidal particles of arsenic, antimony, bismuth and mercury.

The drugs belonging to this group may be classified as follows :—

Class A : Drugs used in Malaria
Cinchona and its alkaloids, **Pamaquin, Mepacrine, Proguanil** (**Paludrine**), **Chloroquine, Pentaquine, Camoquin**

Class B : Drugs used in Syphilis
Mercury, Bismuth, Arsenic, Iodides, Penicillin

Class C : Drugs used in Leishmaniasis
Antimony and its compounds, Stibophen, Stilbamidine

Class D : Drugs used in Trypanosomiasis
Tryparsamide and other Pentavalent compounds of Arsenic, Suramin

Class E : Drugs used in Amoebic infection
1. Ipecacuanha, Emetine, Emetine-Bismuth-Iodide
2. Certain Organic Arsenic Compounds : Acetarsol, Carbarsone
3. Kurchi and its alkaloids (*q. v.*)
4. Oxyquinoline Derivatives and certain Dyes : Chiniofonum, Quiniodochlorum (Entero-Vioform), Diodoquin, Rivanol
5. Chloroquine, Aureomycin

Class F : Drugs used in Bacterial invasions
1. Sulphonamide group.
2. Antibiotics : Penicillin, Streptomycin, Chloramphenicol, Aureomycin, Terramycin and Tyrothricin

Class G : Drugs used in Tuberculosis
Para-aminosalicylic Acid, Streptomycin, Thiacetazone, Gold

Class H : Drugs used in Leprosy
Hydnocarpus Oil, Chaulmoogra Oil, Sulphones

Class I : Drugs used in Helminthic infections
See Anthelmintics, page 389

Class A : Antimarial remedies

Osler's oft quoted dictum that malaria is probably the greatest single destroyer of the human race is by no means exaggerated. It has been estimated that in India malaria is directly responsible for over one million deaths per annum. On a conservative estimate India requires somewhere about 1,250,000 lbs. of quinine annually but the actual consumption is only about 200,000 lbs. of which, about 70,000 lbs. are produced in India. It follows, therefore, that one cannot depend upon quinine alone to tackle the problem of malaria in India, some form of alternative drugs have to be found, either to replace or supplement quinine.

Prior to the World War of 1914-1918, the only anti-malarial drugs available were the cinchona alkaloids, of which, the most extensively used was quinine. The shortage of quinine in Germany during this period stimulated research to find synthetic anti-malarial remedies. Of these Plasmoquine (Pamaquin) was introduced in 1925 and was found effective against the asexual forms of benign tertian and quartan malaria, but the doses which produced this effect were found to be toxic. Since it destroys the gametocytes of *P. falciparum* in small doses, it is of great value as a prophylactic by preventing dissemination of infection through infected mosquitoes. It also acts on the parasite during the tissue phase but in doses which produce toxic manifestations. The next advance was the introduction of Atebrin (Mepacrine) in 1932. It acts on the asexual forms of all species of malaria parasites but has no effect on the gametocytes of malignant tertian infection or on the exo-erythrocytic forms.

During the second World War an intensive search for anti malarial remedies was carried out both in the United Kingdom and America with the result that a number of anti-malarial remedies have been synthesised and intro-

duced under various trade names. In 1944 Paludrine (Proguanil) was discovered by a band of British Scientists and found to be effective specially during the tissue phase of the falciparum infection. Side by side the American workers introduced several drugs, viz. Chloroquine, Pentaquine, Camoquin, etc., which give promise of usefulness and have added to the armamentarium of the physician.

Of the different anti-malarial drugs quinine, pamaquine, chloroquine, pentaquine and camoquin contain quinoline ring, whereas mepacrine is an acridine dye and structurally not related to quinine. Proguanil is a biguanide of a pyrimidine derivative distinct from acridine and quinoline derivatives. While quinine, proguanil, mepacrine, chloroquine and camoquin act against asexual forms of the parasites and are used for clinical cure, some of these, like mepacrine, proguanil and chloroquine have also been used as suppressants. Chloroquine is less toxic and more effective than mepacrine and does not stain the skin.

The discovery that the malaria parasites instead of passing through two phases, *i.e.* asexual and sexual cycle of development, also undergo development in the parenchymal cells of the liver (pre-erythrocytic phase) brings into prominence the importance of a drug or combination of drugs, which will produce a chemotherapeutic action against the parasites not only when they are free in the peripheral blood but also during their sojourn in the solid tissue. Such a drug will prevent the development of schizonts and thus will act as a prophylactic when given during the incubation period and prevent relapse when used as a curative agent. So far no drug has been found which acts on the sporozoites.

Antimalarial drugs are used for the following purposes, viz. (*a*) as prophylactic. Here the drug must act on the parasites before they enter the red blood cells, therefore, it must act either on the sporozoite or on the exo-erythrocytic forms ; (*b*) as suppressants. By this clinical manifestations are kept in abeyance, but do not prevent the mosquitoes from infecting man ; (*c*) as curative agent.

It has been found in practice that infection with *P. falciparum* presents little difficulty since it can almost entirely be prevented by regular use of one or other of the anti-malarial drugs, and eradicated if treatment is given early and before there is any cerebral involvement. It should also be recognised that certain strains are amenable to quinine while others to mepacrine or proguanil. The real problem is the treatment of *P. vivax* infection and the drug which will in all cases completely eradicate it has yet to be found. In fact no single drug given alone will in all cases cure completely or prevent relapse. Quinine, pamaquine, proguanil, mepacrine, alone or in combination,

have all been tried. Pentaquine shows the lowest relapse rate when used singly but more clinical observation is necessary before final verdict can be given. On the other hand its toxicity is about one half to one quarter to that of pamaquine.

Inspite of the fact that great advances have been made during recent years and new lines for experimental approach for further research have followed the discovery of exo-erythrocytic forms in the liver, the problem of malaria control has not been solved, although anti-malarial treatment may be said to be better than before. Instead of depending on one drug, *i.e.* quinine, there are now available several alternative remedies. While it is true that most of the new synthetic drugs now in use have to a certain extent solved the problem, quinine still remains the sheet anchor during an emergency.

Since the parasites undergo development in the solid tissue during the incubation period and in the red blood cells during the asexual phase, it follows that there must be some substance in these situations essential for the metabolism of the parasites. Whether this metabolite is porphyrin, riboflavin, or *p*-aminobenzoic acid, or some other substance yet unknown, has not been settled. Real solution of the problem of anti-malarial chemotherapy lies in this direction. Efforts are being made to find suitable analogues which will offer competition with the enzyme system, whatever that may be, for the development of malaria parasites and thus inhibit their growth and reproduction.

CINCHONA

Cinchona. (Cinchon.). Not official.

Syn.—Cinchonae Rubrae Cortex; Red Peruvian Bark.

Source.—The dried bark of the cultivated trees of *Cinchona Calisaya*, *Cinchona Ledgeriana*, *Cinchona officinalis*, *Cinchona succirubra*, and of hybrids of either of the last two species with either of the first two. Contains not less than 6 p.c. of the total alkaloids of cinchona, of which not less than one-half consists of quinine and cinchonidine.

Composition.—A. *Four important alkaloids.*—(1) *Quinine.* (2) *Cinchonine.* (3) *Quinidine.* (4) *Cinchonidine.* B. *Three acids.*—(1) *Quinic acid.* (2) *Quinovic acid.* (3) *Quinotannic acid.* C. *One glucoside.*—*Chinovin*, which easily splits up into chinovic acid and glucose. *Cinchona red. One volatile oil* which gives the bark its smell.

Incompatibles.—Ammonia, lime water, metallic salts and gelatin.

Non-official Preparations

1. **Tinctura Cinchonae, B.P.C.**—Contains 1 p.c. w/v of the alkaloids of cinchona, or 3/5 gr. in 60 ms. *Dose.*—30 to 60 ms. or 2 to 4 mils.

2. **Tinctura Cinchonae Composita, B.P.C.**—Contains 0.5 p.c. w/v of the alkaloids of cinchona, or 1/4 gr. in 60 ms. *Dose.*—30 to 60 ms. or 2 to 4 mils.

3. **Cinchonidinae Sulphas.**—In colourless, silky crystals, soluble in 100 parts of water. *Dose.*—1 to 10 grs. or 0.06 to 0.6 grm.

4. **Cinchoninae Sulphas.**—The sulphate of an alkaloid obtained from several species of cinchona. In white lustrous prismatic crystals. Odourless with a bitter taste. *Dose.*—1 to 10 grs. or 0.06 to 0.6 grm.

Cinchona Febrifuge, I. P. L.—Cinchona Febrifuge is a mixture of alkaloids from the bark of *Cinchona Ledgeriana, Cinchona succirubra* and other suitable species of cinchona. Contains not less than 7 p.c. anhydrous quinine and not less than 50 p.c. of total crystallisable cinchona alkaloids including quinine.

Characters.—Nearly colourless pale yellowish-grey, or pale brown powder; odourless; taste, bitter. Almost insoluble in cold water, almost completely soluble in warm alcohol (95 p.c.); partially soluble in ether. A solution in alcohol (95 p.c.) is alkaline to litmus.

Dose.—1 to 10 grs. or 0.06 to 0.6 grm.

Pharmacology and Therapeutics

Internally.—Cinchona bark is an astringent, bitter tonic, a febrifuge and a mild antiperiodic, due to the alkaloids and other ingredients it contains. The crude bark irritates the stomach and bowels. It is often prescribed with other vegetable bitters during convalescence from an acute febrile attack, or along with quinine salts to increase their antiperiodic property. Combined with aromatic spirit of ammonia the compound tincture makes an excellent "Pick-me-up."

Owing to its high quinidine content cinchona febrifuge is specially valuable in benign tertian infection. But owing to the presence of cinchonidine it has the disadvantage of causing vomiting. It is best given two and a half hours after food in *cachets, tablets* or in *mixture* with citric or dilute mineral acid. The vomiting may be checked by the previous use of 10 ms. of solution of adrenaline chloride. With cinchona febrifuge relapses are less, and given with alkalies some consider it more effective than quinine. But according to Sinton it gave 73.1 p. c. relapses in simple tertian infection. Provided its composition is standardized, it is but little inferior to quinine both in the production of clinical and radical cure and is cheaper. In order therefore to supply such a standardized preparation, Totaquina has been introduced. The strength of this preparation even varies, but it is fairly reliable.

TOTAQUINA

Totaquine. (Totaquin.)

Source.—Is a mixture of alkaloids from the bark of *Cinchona succirubra, Cinchona robusta,* and other suitable species of *cinchona*. Contains not less than 70 p. c. of crystallisable cinchona alkaloids, of which not less than one-fifth is quinine. Resembles cinchona febrifuge.

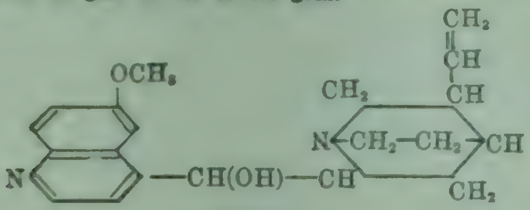
Characters.—A nearly colourless, or pale yellowish-grey or pale brown, powder; no odour; taste, bitter. Almost *insoluble* in water, almost completely soluble in warm alcohol (95 p. c.), partially soluble in solvent ether, almost completely in chloroform.

B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

QUININAE HYDROCHLORIDUM. (Quinin. Hydrochlor.). $C_{20}H_{24}N_2O_2,HCl,2H_2O$.—Quinine Hydrochloride is the hydrochloride of an alkaloid, quinine, obtained from the bark of various species of Cinchona. Contains 81.0 to 83.0 p.c. quinine.

Characters.—Colourless, glistening needles ; effloresces in warm air ; no odour ; taste, very bitter. *Solubility.*—1 in 32 of water, 1 in 2 of alcohol (90 p.c.).

B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.



Quinine

OFFICIAL PREPARATIONS

1. **Injectio Quininae et Urethani.**—Quinine hydrochlor. 12.5 p. c., urethane 6.25 p.c. **B. P. Dose.**—**8 to 75 ms. or 0.5 to 5 mils** ; by intravenous injection as a sclerosing agent.

2. **Tabellae Quininae Hydrochloridi.—B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.** N. B. If the quantity to be contained in a tablet is not stated, 5 gr. tablets shall be supplied.

Quininae Dihydrochloridum. (Quinin. Dihydrochlor.). $C_{20}H_{24}N_2O_2$, 2HCl. **Syn.**—Quinine Acid Hydrochloride.—Quinine Dihydrochloride is the dihydrochloride of an alkaloid quinine.

Characters.—A colourless powder ; odourless ; taste, very bitter. *Solubility.*—In 0.6 parts of water and in 12 parts of alcohol (90 p. c.). Reaction acid.

B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm. By intravenous injection :—**5 to 10 grs. or 0.3 to 0.6 grm.**

OFFICIAL PREPARATION

1. **Injectio Quininae Dihydrochloridi.—B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.** *by intravenous injection.* N. B. When no strength is stated, a solution containing 5 gr. in 15 ms. shall be dispensed. This must be diluted with at least 10 times its volume of injection of sodium chloride before administration and injected slowly.

QUININAE SULPHAS. (Quinin. Sulph.). Quinine Sulphate. $(C_{20}H_{24}N_2O_2)_2$, H_2SO_4, $2H_2O$.

Characters.—Colourless, glistening, silky needles ; taste, intensely bitter. *Solubility.*—1 in 810 of water, giving the solution a bluish fluorescence ; entirely in water acidulated with a mineral acid.

Incompatibles.—Alkalies and their carbonates, astringent infusions.

B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

NON-OFFICIAL PREPARATIONS

1. **Liquor Quininae Ammoniatus, B.P.C.** *Syn.—Tinctura Quininae Ammoniata.*—Contains 2 p.c. w/v of quinine sulphate and 1 p.c. w/v of ammonia, or 1⅓ gr. quinine in 60 ms. *Dose.*—30 to 60 ms. or 2 to 4 mils.

2. **Syrupus Ferri Phosphatis cum Quinina et Strychnina, B.P.C.** *Syn.—Easton's Syrup.*—1.5 gr. quinine in 60 ms. *Dose.*—30 to 60 ms. or 2 to 4 mils.

Quininae Bisulphas. (Quinin. Bisulph.). **Syn.**—Quinine Acid Sulphate.—Quinine Bisulphate is the bisulphate of the alkaloid quinine.

Characters.—Colourless, transparent or opaque, small needles. Odourless ; taste, bitter. Becomes yellow when exposed to light. *Soluble* in 10 parts of water, in 2[illegible] parts of alcohol (90 p.c.). Solution strongly acid to litmus.

B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

OFFICIAL PREPARATION

1. **Tabellae Quininae Bisulphatis.** *Syn.—Tablets of Quinine Acid Sulphate.* **B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.** N. B. If the quantity to be contained in a tablet is not stated, 5 gr. tablets shall be supplied.

Quininae et Aethylis Carbonas. (Quinin. et Aethyl. Carb.). **Syn.**—Euquinine ; Tasteless Quinine.—Quinine Ethyl Carbonate is prepared by the action of ethyl chlorocarbonate on quinine.

Characters.—Fine, soft, white matted needles ; odourless ; almost tasteless. Darkens on exposure to light. Slightly *soluble* in water, soluble in 2 parts of alcohol (90 p.c.), readily in dilute acids.

B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

Non-official Preparations

1. **Quininae Hydrobromidum, B.P.C.**—In white acicular crystals soluble in 55 parts of boiling water. With excess of diluted hydrobromic acid it lessens cinchonism. *Dose.*—1 to 10 grs. or 60 to 600 mg.
2. **Quininae Lactas.**—A crystalline or granular white powder soluble in 6 parts of water. Suitable for hypodermic use. *Dose.*—1 to 5 grs. or 60 to 300 mg.
3. **Quininae Salicylas, B.P.C.**—Silky crystals, sparingly soluble in water. In *rheumatism, neuralgia, and diarrhoea. Dose.*—1 to 5 grs. or 60 to 300 mg.
4. **Quininae Acetylsalicylas.** *Syn.*—*Quinine Salacetate.*—In white crystalline powder, 64 p.c. of quinine. *Dose.*—1 to 5 grs. or 60 to 300 mg.
5. **Quininae Valerianas, B.P.C.**—In *nervous headache* and *hysteria. Dose.*—1 to 3 grs. or 60 to 200 mg.
6. **Warburg's Tincture.** *Syn.*—*Tinctura Antiperiodica.*—Contains quinine sulphate about 4½ grs. in 4 drs. *Dose.*—1 to 4 drs. or 4 to 16 mils.
7. **Aristochin.** *Syn.*—*Aristoquinine.*—The neutral carbonic ester of quinine in white tasteless powder. Insoluble in water. *Dose.*—1 to 10 grs. or 0.06 to 0.6 grm.
8. **Quininae Tannas, B.P.C.**—Contains 27 to 35 p.c. anhydrous quinine. A pale-yellow or yellowish-white, amorphous powder ; taste, slightly bitter, astringent. *Dose.*—1½ to 15 grs. or 0.1 to 1 grm.

Pharmacology

Externally.—The characteristic action of quinine alkaloid is its effect on undifferentiated protoplasm, and it is an active poison to many low forms of vegetable and animal life. Ciliary movements cease and according to Binz a solution of 1 in 20,000 destroys paramecia and amoeba. Spermatozoa and ova are destroyed by smaller strengths, and in strengths of 1 in 10,000 spirochaeta of vegetable decomposition become motionless, but those of relapsing fever are not influenced by strengths even of 1 in 500.

Quinine and its derivatives have also a marked anaesthetic action with somewhat prolonged latent period, but the resulting anaesthesia is of longer duration. This anaesthetic action may be possibly due to necrosis of the axis cylinders and sheaths with subsequent regeneration.

Internally. **Mouth.**—It is a pure bitter, and has an intensely persistent bitter taste if taken in neutral or slightly acid solution, as the alkaline saliva precipitates the alkaloid. Like other bitters it reflexly stimulates the salivary secretion by exciting the gustatory nerves. The tannate is less bitter and the ethyl carbonate is almost tasteless.

Stomach and intestine.—All the cinchona alkaloids have a marked inhibitory effect on the peptic and tryptic digestion. Cinchonine is the most powerful, hence this alkaloid cannot be tolerated for long when taken by the mouth. The monosalts inhibit peptic digestion still further as they use up most of the available free hydrochloric acid to form the more soluble disalts. Quinine for the most part passes through the stomach unchanged and reaches the duodenum, where the alkaline contents precipitate it as nascent alkaloid which is soluble in bile, and it is only in this form that quinine is absorbed. The absorption is retarded if it is given soon after or with meals. Three things are necessary for its absorption, *viz.*, (*a*)

solubility in the stomach ; (*b*) alkalinity in the duodenum; and (*c*) available bile. The tannate and the ethyl carbonate are absorbed very slowly as they require to be hydrolysed by the alkali of the duodenum.

In small doses (1 to 2 grs.) it is a bitter and stomachic like calumba, and indirectly acts as a general tonic. In large doses (15 to 40 grs.) it produces the opposite effects —depression and gastro-intestinal irritation.

Blood.—In whatever form quinine is given it circulates as quinine base and is present in the plasma, adsorbed on to the surface of the red blood-cells, but not within them. Therefore those parasites that have become intracellular escape from its effect. Its concentration in the blood varies. With a dosage of 0.3 grm. (5 gr.) the concentration is between 0.2 to 0.9 mg. per 100 mil; with 0.2 grm. (3 gr.) it is about 0.3 mg.; for 0.5 grm. (8 gr.) it is 0.5 mg.; and for 1.5 grm. (23 gr.) 1 mg. in 100 mil. Higher concentration is associated with toxic reaction. After absorption into the blood quinine has several specific actions which may be described under the following heads:—

1. *White corpuscles.*—After small doses of quinine there is some lymphocytosis, possibly due to contraction of the plain muscles of the spleen. After large doses this is followed by a reduction in the number of leucocytes, the lymphocytes being more reduced than the polymorphonuclears. This phase is again followed by leucocytosis, the polynuclear cells being only increased.

2. *Red corpuscles.*—These are not materially affected, though many assert that it increases their number and causes an increase in their size. Haemolysis occurs only when quinine circulates in the blood in sufficient concentration to cause arrest of the heart, *i.e.* 0.5 p.c. Therapeutically this concentration is not attained. Haemoglobinuria observed in some patients undergoing treatment is possibly due to idiosyncrasy.

Biology of malaria parasites.—The causal organisms of malaria belong to the genus *Plasmodium*, which belongs to the class of the protozoa known as sporozoa. Four species are generally recognised as being concerned in the production of human malaria, *viz.*—*Plasmodium vivax*, the parasite of benign tertian malaria ; *Plasmodium falciparum*, the parasite of malignant or subtertian malaria ; *Plasmodium malariae*, the parasite of quartan malaria ; and *Plasmodium ovale*, a parasite which produces a mild type of tertian malaria in Africa.

The malaria parasites (sporozoites) when introduced into the body do not circulate in the blood but disappear from the general circulation and enter the solid tissues (the parenchymal cells of the liver) when they are called cryptozoites and subsequently become cryptomerozoites

and undergo a series of developmental changes—primary exo-erythrocytic stage (tissue phase). During this period the patients do not show any symptoms or signs of disease nor any parasite in the blood. After this period of incubation ranging from 10 to 14 days the cryptomerozoites are released as pre-erythrocytic merozoites, which enter the red blood-cells as trophozoites within which they undergo asexual cycle of development and begin their erythrocytic phase giving rise to clinical attack of malaria.

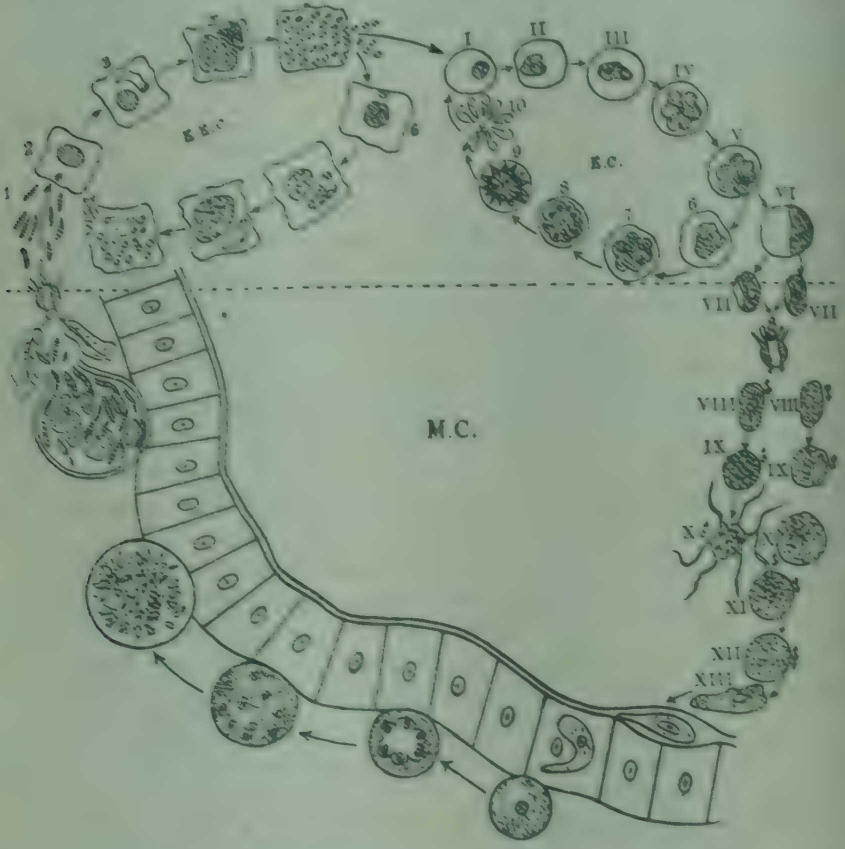


Fig. 33.—The Life Cycle of Malaria Parasite.

The portion below the dotted line shows the sexual cycle within the body of the mosquito. The portion above is the human cycle which consists of two phases or cycles, viz. exo-erythrocytic cycle (E. E. C.) and erythrocytic cycle (E. C.).

1. Infected mosquito introduces sporozoites which enter the liver cells.
2, 3, 4. Stages of development of pre-erythrocytic schizonts in the liver cells.
5. Fully developed pre-erythrocytic schizonts rupturing and liberating pre-erythrocytic merozoites. (6) These enter fresh liver cells and go through second generation as secondary exo-erythrocytic stage.
I. Exo-erythrocytic merozoites entering the red blood corpuscles.
II-V. Development of trophozoites in circulating blood.
6-9. Trophozoites developing into schizonts.
10. Fully developed schizonts rupturing and entering fresh red-blood corpuscles.
VI. Some trophozoites develop into VII gametocytes. VIII. Male and female gametes fertilizing within the stomach of the mosquito and pass through different stages and form sporozoites which enter salivary glands of the mosquito and inject into the human body during a bite.

he corpuscles containing the schizonts rupture and set free he new merozoites to begin the next phase, provided these erozoites are not killed when free in the peripheral blood.

Some of the cryptomerozoites instead of entering the ed blood-cells enter the normal liver cells and continue eir development as secondary exo-erythrocytic cycle. his process may repeat itself indefinitely irrespective of hether the erythrocytic cycle is present, or held in check ither as the result of treatment, or as the result of naturlly acquired immunity. This immunity, however, is ffective against merozoites which are destined to enter he red blood corpuscles, while those which enter liver cells o maintain secondary exo-erythrocytic cycle are probably rotected from destructive effects of immunity by their ntracellular habitat. When the active immunity of the uman host becomes diminished in time, it has little effect n those merozoites which are destined to recommence the rythrocytic cycle, therefore these enter the red bloodorpuscles and produce the clinical picture of relapse.

The exo-erythrocytic forms are known to occur in lmost every type of avian malaria and are found in endohelial cells in the tissues. They occur as a stage between he sporozoites introduced by the infected mosquito, and he parasites which eventually develop within the erythrortes, but they may also persist throughout the time the fection lasts, and serve as a reservoir from which paratics may be released to invade more blood corpuscles.

Recently Shortt, Garnham, Covell and Shute * have nown presence of pre-erythrocytic stage of human alaria, *Plasmodium vivax*, in the liver of human beings.

Specific action.—In order to prevent malaria a drug ust act on the parasites before it enters the red blood lls, *i.e.* during the incubation period. To achieve this d a drug must act either on the sporozoites or on the exorythrocytic forms, *i.e.* during the tissue phase. No drug known which will kill the sporozoites, but proguanil aludrine) acts as a causal prophylactic in malignant rtian malaria, *i.e.* will kill the exo-erythrocytic forms.

Quinine 1 in 10,000 solution inhibits the amoeboid ovements of the plasmodium *in vitro*. Under quinine the arasites disappear from the peripheral circulation, when a result of schizogony the young parasites are set free the blood plasma. A few of the more resistant type cape and multiply and eventually provoke another aroxysm of fever. After the parasites have entered the rpuscles they become resistant to quinine except the ss dangerous forms. Quinine has no effect on sporoites even in high concentrations, nor has it any action

* *British Medical Journal*, March 20, 1948.

on the crescents and therefore mosquitoes can readily b infected even though the patient may be taking quinin The exact manner in which it cures malaria is far from settled.

Since the drug is rapidly excreted it cannot have any direct ac tion on the plasmodia. In fact the concentration in the blood even whe given in full doses does not exceed 1 in 100,000 and this concen tration does not kill the parasite in *vitro*. It has therefore bee suggested that the action is indirect, and that the effective therapeut agent may be a metabolite formed by the breakdown of the quinin in the tissue, though no evidence of such a metabolite has been traced Yorke and Macfie maintain that the real action depends upon th capacity of the host to form an immune body in response to the anti gen formation resulting from the destruction of a large number o parasites by the medicament. The evidence in favour of the forma tion of an antibody is however rather meagre. Morgenroth believe that the parasites are unable to enter the red blood corpuscles which are made resistant against penetration thus making the parasites un able to multiply.

It is possible that several factors contribute towards the cure of malaria, the one that plays the predominant part is the capacity of the cells of the reticulo-endothelial system to respond to the stimulus of infection by mobilisation, proliferation and functional activation. Administration of quinine merely heightens these responses, and when they are adequate the disease is overcome. The factors such as the direct action of the drug on the parasite and infected red cells, as well as biochemical and other alterations in the serum, help to augment the efficiency of the phagocytic mechanism to varying extent.

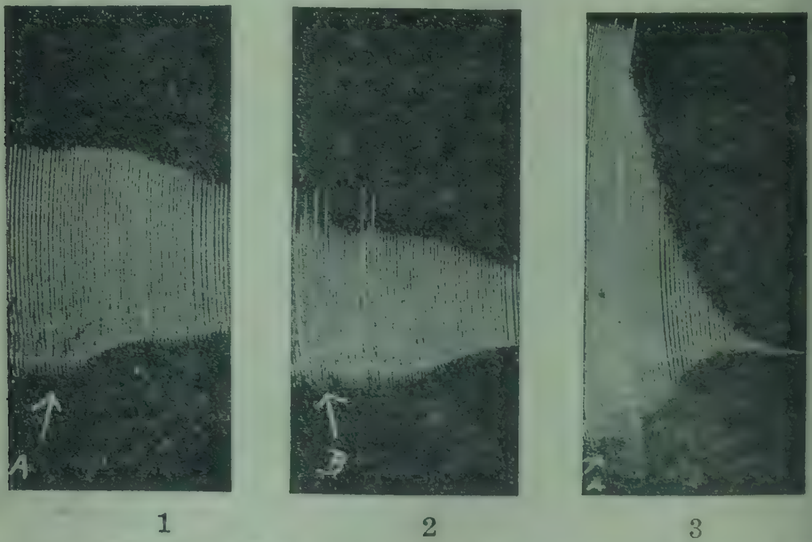


Fig. 34.—Showing effect of Quinine on Isolated Rabbit's Heart perfused with Locke's solution.

1. Shows the effect of small dose ; 2. shows the effect of a higher dose. Note more powerful depressant effect on the heart ; 3. shows the effect of a large dose. Note the profound depressant effect making the contraction weaker and slow, and the heart eventually stops.

Heart and circulation.—Small doses reflexly stimulate the heart through the stomach, but large doses given intravenously directly paralyse it ; the pulse becomes slow and

feeble, and at last the heart stops in diastole. These effects are not observed when quinine is given by the mouth even in large therapeutic doses and are due to direct action of the drug on the cardiac muscle. With weakness of the heart the blood pressure falls. Intravenous injections cause a sharp and often dangerous fall of blood pressure from cardiac weakness and peripheral vaso-dilatation due partly to central effect and partly to direct action on the muscle of the vessel.

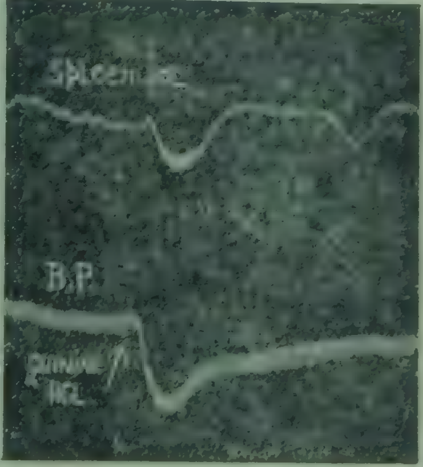


Fig. 35.—Dog., paraldehyde. Record of the effect of quinine hydrochloride on blood pressure and spleen volume. Note fall of blood pressure and also of spleen volume.

Respiration.—It is not affected by small doses, but is quickened by moderate doses, and in toxic doses it becomes slow and weak and then arrested. The gaseous interchanges are checked.

Liver and spleen.—It has no action on the liver, but contracts the recently enlarged spleen rather by destroying the malarial parasite, and so preventing accumulation of the irritating products—pigments, etc., and reduces the hyperaemia.

Metabolism.—Quinine and its derivatives were formerly believed to depress metabolism. But observations made by Hardikar have failed to show any alteration in the protein metabolism either in man or in animals.

Temperature.—Quinine has very little effect upon the temperature in health, but causes a marked reduction in fevers, particularly if they are of malarial origin. It is therefore an antipyretic in malaria. It sometimes lowers the temperature in fevers of non-malarial origin, but the precise mode of its action has not been definitely settled. It was formerly believed that this effect was due to its action on the metabolism. But the amount of quinine which lowers the temperature has no appreciable effect on the metabolism. It is possible that it acts on organisms other than malarial parasites. Its action is like other antipyretic drugs and is due to adjustment of the heat regulating centres, whereby there is increased heat loss from cutaneous vaso-dilatation and lessened heat production (*Hardikar*, 1925 and *Virchow*, 1927).

Skeletal muscles.—Quinine increases the refractory period of the voluntary muscles so that the effect of tetanus is diminished. It also diminishes the excitability of

the muscle to electrical stimuli and possesses a curara like action. It blocks the action of acetylcholine and is anatgonistic to neostigmine. For these reasons it has been used in myotonia congenita (Thomsen's disease) in $2\frac{1}{2}$ to 15 grs. doses, twice or thrice daily.

Nervous system.—Small doses have a tonic effect upon the nervous system, but large doses produce a train of symptoms known as cinchonism. Frequently there is impairment of the sense of hearing and perhaps of the sight. Ringing in the ears and slight deafness are noticed even after moderate doses. Sometimes there is complete loss of hearing, which disappears in a few days. Dimness of vision and sometimes total blindness may be present, and the patient may become colour blind. It has been thought that the ear symptoms are due to degenerative changes in the spiral ganglia of the cochlea.

The effects on the brain are not uniform. Some complain of fullness and heaviness of the head, while in others there is motor excitement with convulsion and delirium. Weakness of the heart and muscles, apathy, impairment of sight and hearing with unconsciousness and failure of respiration are observed in fatal cases.

Injected into animals it causes transient excitement of the central nervous system, but the real effect is depression. The cord is first stimulated and then depressed in mammals. The respiration first becomes quick but subsequently weak and slow, death occurs from respiratory failure. Tremors and convulsion before death are possibly due to asphyxia.

Uterus—Quinine occasionally acts as an ecbolic and it certainly intensifies the labour pains or re-establishes them if they are absent, when parturition has commenced. Menstruation is sometimes induced by quinine in non-pregnant women. Metrorrhagia is an occasional symptom, although given after labour it often stops haemorrhage.

Quinine in sufficient concentration causes contraction of uterine muscle in the non-pregnant uterus, *i.e.* after large doses. During pregnancy much depends on the state of the uterus. Large doses (15 to 30 grs.) cause increase in the *intermittent* uterine contractions, and, in the presence of weak membranes, open the os and precipitate labour. Larger doses throw the uterus into a state of tonus. In malarial fever there is a greater danger from the foetus dying as the result of the high temperature caused by the disease. So quinine must be given promptly and immediately, and as long as the doses are sufficiently small (2 to 5 grs. every few hours), and not more than 30 grs. are given during the course of twenty-four hours, there is no danger of ecbolic action of this alkaloid.

Absorption and clearance.—Quinine is absorbed by the

duodenum and circulates in the blood as quinine base. Soluble salts are absorbed more quickly, but the rate of absorption varies in different people. Given in solution it appears in the urine very quickly ; about 20 p.c. being eliminated either unchanged or conjugated with glycuronic acid. Quinine however does not circulate in the blood for a long time in any concentration ; after an intravenous injection about 90 to 95 p.c. disappears within 5 minutes. The concentration of quinine in the blood varies even with the same oral dose. A concentration of 0.5 mg. per 100 mil for 4 days will cause disappearance of the parasite for 14 days. Excretion of quinine varies greatly in different individuals and from day to day. It may be detected in the urine half an hour after administration, and excretion may go on for 48 hours or even 72 hours, the remainder undergoing destruction in the tissues. Any that is stored in the body will probably be found in the suprarenal bodies and the spleen, which organs are incapable of destroying it. Administered per rectum absorption is poor, irregular and unreliable and may cause irritation.

Toleration.—Some persons are very susceptible to the action of this drug. When a small dose produces headache and ringing in the ears, it is due to *idiosyncrasy*.

The role of quinine in the production of black water fever has not yet been definitely settled. A case of death following the administration of fifteen grains of quinine has been reported, the symptoms leading to this result being profuse internal and external haemorrhage.

Therapeutics

Internally.—As a *stomachic* it is very useful in convalescence from an acute illness, particularly malarial fever. Its efficacy is increased if it is combined with mineral acids and other bitters.

As an *antipyretic* it is inferior to phenazone, phenacetin, or sodium salicylate.

Malaria.—In malaria three methods of treatment may be followed, namely, prophylactic treatment destroys the parasites in the primary exo-erythrocytic phase ; curative treatment eradicates the secondary tissue phase ; and suppressive treatment eradicates the erythrocytic parasites and thus prevents clinical attack as long as the drug is continued.

In the treatment of malaria a single dose of 10 grs. or two doses of 10 grs. every two or three hours should be given at least two hours before the expected paroxysm. It will then be absorbed into the blood in sufficient concentration and will quickly attack the young merozoites when they are free in the plasma and before they are able to enter the red blood corpuscles. It is probable that during this

stage these asexual parasites are most susceptible to the effect of quinine. Sometimes, however, it may not be possible to give sufficient doses of quinine before the next paroxysm. In such cases it should be started when the temperature begins to fall so that a total quantity of 20 to 25 grs. in two or three doses can be given before the expected paroxysm. In every case the physician should be guided by the severity of the case and quinine should be given at once without any reference to temperature in all cases of malignant infection or when there is danger of waiting for the temperature to fall.

Whenever possible quinine should be given after the bowels have been opened, preferably by a dose of calomel and a saline. But this should be regarded as a matter of convenience and not of routine and no time should be lost in giving quinine once the case is diagnosed as of malaria. After the first or second dose, the question of giving a purgative may be considered.

The treatment requires to be stopped after five to seven days in acute attacks, and if the patient has a recrudescence, then it should be given again for the same period or until the symptoms or the parasites disappear. It should not be used during the period the patient's blood is parasite-free. It should be noted that relapses are more common with benign tertian infection than the malignant one, which if properly treated rarely causes relapse. It has been found that relapses are less common when the body is able to develop the natural power of resistance and this is helped by the administration of quinine with iron and arsenic.*

The routine treatment followed by the writer is to give 10 grs. of quinine with $2\frac{1}{2}$ grs. of acid acetylsalicylic in cachets as the first dose when the temperature is beginning to fall, followed by two more doses every three hours; the second and the third doses contain $7\frac{1}{2}$ grs. of quinine instead of 10 grs.† If the paroxysm is not checked the treatment is repeated the next day but the second dose should contain 10 grs. of quinine. This usually checks the fever and the same procedure is followed for three to four days after the temperature has become normal. If no more attacks occur the use of quinine should be stopped for at least one week. The writer is satisfied with this treatment and rarely had relapses. The success depends upon giving enough quinine, *i.e.* not less than 20 to 30 grs. within four to six hours, so that it will be absorbed and

* Acid. hydrochlor. dil.	ms. 10
Ferr. et quinin. cit.	grs. 10
Liq. arsen.	ms. 3
Tinct. nuc. vom.	ms. $7\frac{1}{2}$
Mag. sulph.	grs. 60
Glycerin.	ms. 20
Aq. menth. pip. dest. ad.	oz. 1

† Quinin. hydrochlor.	grs. $7\frac{1}{2}$
Acid. acetylsalicyl.	grs. $2\frac{1}{2}$
Calc. lact.	grs. $7\frac{1}{2}$

circulate in the blood in sufficient concentration when the parasites are free in the blood and before the appearance of the expected paroxysms. Besides relieving many unpleasant symptoms and acting as a cholagogue and antipyretic, aspirin helps the action of quinine.

Sinton has pointed out that there exists some similarity between an attack of malaria and an anaphylactic shock, caused by the absorption of foreign protein from the body of the malarial parasite. Alkalies and magnesium sulphate given along with quinine treatment relieve the condition. He believes that the alkali has a catalytic effect on the action of quinine on the plasmodium and helps to lower the hydrogen-ion-concentration of the blood. The method of treatment is as follows : On the first day 3 grs. of calomel and 1 oz. of magnesium sulphate are given ; on the following day 60 grs. of sodium bicarbonate and 40 grs. of sodium citrate dissolved in 1 oz. of water is given for three doses every two hours ; followed after half an hour by 10 grs. of quinine sulphate, 20 grs. of citric acid and 60 grs. of magnesium sulphate in 1 oz. of water. By this method 60 to 180 grs. of quinine can be given within a week. Sinton claims that this method of treatment yields much better results than when quinine is given without an alkali.

The oral administration is the simplest and most practicable and should be the method of choice. An agreeable method of giving quinine in solution to patients with gastric irritation or to fastidious persons is in the form of effervescent mixtures.* The intramuscular method is rarely required unless there is vomiting and other contraindications to oral use or when oral route is not attended with any success. In any case not more than two injections need be given. The intramuscular injections are given indiscriminately and often in cases where quinine is not indicated. This method is painful and may sometimes be followed by severe necrosis. The danger, however, appears to have been exaggerated. The intravenous route should be used only in pernicious cases and when immediate action is essential, as for instance, in cerebral malaria. The dihydrochloride in 10 gr. doses dissolved in 10 to 20 mils of physiological saline solution should be used, and the injection made very slowly so that it will reach the heart in low concentration ; at least three minutes should be spent over the operation. Where the blood pressure is low add 2 to 3 drops of injection of adre-

(1) * Quinin. hydrochlor. gr. 7½
Acid. cit. gr. 15
Syr. limon. ms. 30
Aq. chlorof. ad. oz. 1

(2) Sod. bicarb. gr. 20
Sod. cit. gr. 20
Aqua ad. oz. 1/2
One dose of each to be mixed and taken during effervescence.

naline to prevent further and possibly a fatal fall in the pressure.

In chronic malarial fever with relapses, anaemia and enlarged spleen quinine is best given in combination with iron and arsenic either in the form of a mixture or in pill form.*

(2) *Enlargement of the spleen.*—With the cure of malaria the size of the spleen is reduced, but the efficacy of quinine is greatly augmented if it is given with iron.†

(3) *Malignant form of malarial fever.*—Many deaths occur from this type of fever from want of courage on the part of the physician to administer quinine in sufficiently large doses. From the beginning without any reference to temperature or local symptoms, with stimulants if necessary, quinine should be given. Although it is well recognised that malignant malaria reacts quickly to quinine, it has been found that certain strains of this parasite in special localities are resistant to it, which can be successfully cured by proguanil (paludrine) or mepacrine. Malignant tertian malaria, associated with persistent vomiting or threatened coma, should be treated with intravenous quinine.

In the *so-called malarial cachexias*, especially those of *the haemorrhagic type*, quinine is of questionable value. Quinine base has *no haemolytic action.* If the effect in "black water fever" is real it must be due either to (i) decomposition product of quinine, or (ii) aiding the formation of haemolysin.

(4) *Intermittent* or *remittent neuralgias* of malarial or non-malarial origin, often yield to quinine.‡

As regards *prevention of infection*, there is no evidence that the use of quinine is of any effect. But the term "prophylaxis" in relation to malaria is frequently employed to mean the prevention of clinical symptoms following infection and for this purpose it undoubtedly has its uses. Quinine prophylaxis in this sense has proved of great benefit in the case of prisoners in jails and when given to troops serving in malarious countries, and it has been found that the systematic quininisation of school children greatly reduces the spleen rate. In the case of threatened epidemic of malaria the prophylactic use of quinine will save many lives whilst in any malarious community it will have good effect by reducing the number of human carriers of benign tertian malaria, though it has no effect on the gametocytes

*Arsen. trioxid.	gr. 1/24
Quinin. sulph.	grs. 2
Pulv. ipecac.	gr. 1/6
Ferr. sulph.	gr. 1
Ext. nuc. vom. sicc.	gr. 1/4
Pil. rhei. co.	grs. 1½

†Quinin. sulph.	grs. 2
Ferr. sulph.	grs. 2½
Pulv. rhei.	grs. 5
Pulv. ipecac.	gr. 1/6
Sod. bicarb.	grs. 2½
In powder or cachet.	

‡Quinin. hydrochlor.	grs. 5
Phenacetin	grs. 2½
Caffein. cit.	grs. 2

of malignant tertian (crescents). It is particularly necessary that the quinine should be administered to children, who form the principal reservoir of the disease. The most effective dose for prophylactic purposes is 10 grs. daily, but it is seldom possible to do this and it is more usual to give 10 to 15 grs. twice weekly. The drug is best given in solution, but it is frequently impossible to give it in this way on a large scale. If tablets are used, the form of the salt used should be the dihydrochloride, and these should be fresh and their solubility tested before use.

As an *ecbolic* it is prescribed in uterine inertia during labour, if there is no obstruction. Ten grains followed by a similar dose after one or two hours often strengthen weak pains.

As a *nervine tonic* it has been used with benefit in a host of nervous diseases, generally in combination with iron and strychnine, as Easton's syrup.

Quinine in pregnancy.—Much confusion appears to exist regarding the use of quinine in this condition because of its ecbolic effect. As has been pointed out, there is more danger of abortion in an untreated case of malaria than when properly treated with quinine. Quinine should therefore be given irrespective of pregnancy and the patient carefully watched. In any case the dose should not be more than 5 grs. at a time and this dose will rarely excite uterine contraction. In patients with a sensitive uterus, or if there be any history of previous abortion or miscarriage, it should be combined with or followed by either potassium bromide, or, according to the urgency of the case, with a preparation of opium. In case of doubt use mepacrine or proguanil.

Other Uses.—In combination with urethane (Injectio Quininae et Urethani), quinine is largely used in the injection treatment of **varicose veins.** Urethane helps the solution of quinine and produces an anaesthetic effect. The method is to insert the needle of the syringe into the lowest segment of the vein after the part has been cleaned, and to inject slowly after a little blood being allowed to flow into the needle. Keep the needle for 30 seconds, then withdraw and seal the puncture with collodion and wool, or strap it. The initial dose is 0.5 mil increased to 2 to 3 mils. Pregnancy, acute phlebitis, deep thrombosis, skin diseases, diseases of the heart with failing compensation and renal disease are contra-indications. It should not be given during menstruation. Similarly, it may be used in the treatment of hydrocele.

Untoward effects.—Quinine sometimes gives rise to certain unpleasant symptoms, *viz.*, ringing in the ears with impaired hearing and vertigo; irritation of the bladder with frequent urination, common in old persons; haemoglobinuria; contraction of the uterus and abortion in pregnant women; vomiting; itching, sometimes erythe-

matous, papular or urticarial rash (these often appear after small doses and are due to idiosyncrasy); rarely profound collapse.

Caution.—Quinine should be avoided, or given very cautiously, in acute or subacute disease of the middle ear, gastro-enteritis, extreme anaemia, active cerebral congestion, skin eruptions, such as erythema, urticaria, etc., black water fever, and to persons particularly susceptible to its influence.

Prescribing hints.—The routine method of giving quinine is by the mouth and preferably in solution. Plain tablets are absorbed easily unless they are made with a menstruum which may interfere with their solubility in the stomach. Mineral acids (1 m. to each grain) and solution of ferric chloride dissolve the sulphate, but unless an excess of acid is used, it will leave a persistently bitter after-taste. To avoid this it may well be given in an effervescing form dissolved in citric acid (*see* page 487), or simply suspended in water. To diminish cinchonism the sulphate may be dissolved by the aid of dilute hydrobromic acid in the proportion of 2 ms. of the acid for each grain of quinine. The after-taste of quinine is soon removed or not perceived at all if the patient swallows a little water after taking the drug, and chews a few bits of betel-nut, myrobalan (*haritaki*), unripe guava, or any other substance containing tannin. For children relatively large doses are required, and they tolerate quinine better; quinine ethylcarbonate and aristochin being tasteless should be preferred.

Quinine is incompatible with the usual alkaloidal precipitants. The sulphate is sparingly soluble in water and requires a dilute mineral acid for its solution. With vegetable astringents it forms an insoluble tannate of quinine. With salicylate of soda it forms an ugly looking mass (salicylate of quinine) which requires an addition of some mucilage.

If there is much gastric irritability, intramuscular injection may be given first, followed by the bi-salt by mouth. The intravenous injection should be resorted to only in case of extreme urgency. It should be the method of choice in cerebral malaria. The antiperiodic virtue of quinine is greatly enhanced if combined with aspirin, because of the secretion of bile which has a great solvent action on quinine. Totaquina* may be administered in the form of powder, cachet, pill or in solution with citric acid. As it contains all the cinchona alkaloids it is of great value in benign tertian infection, where it acts better than quinine, but owing to the presence of cinchonine and cinchonidine it is more liable to produce gastric irritation and headache.

The strictest asepsis must be maintained when giving a hypodermic injection of quinine. Several cases are on record where tetanus followed from its use.

QUINIDINAE SULPHAS. (Quinidin. Sulph.).—Quinidine Sulphate is the sulphate of an alkaloid, quinidine, obtained from the bark of various species of Cinchona.

Characters.—Colourless, needle-like crystals; taste, very bitter. Darkens on exposure to light. *Soluble* in 90 parts of water and in 10 parts of alcohol (90 p. c.).

B. P. Dose.—1 to 5 grs. or 60 to 300 mg.

PHARMACOLOGY AND THERAPEUTICS

Internally.—Quinidine is used in malaria specially in the treatment of **benign tertian** infection.

Heart.—It is largely used in the treatment of **auricular**

*Totaquin.	grs. 7½
Acid. cit.	grs. 10
Syr. limon.	ms. 60
Aq. chlorof.	ad. oz. 1

fibrillation, specially when there is no cardiac enalrgement or valvular disease. In about 50 p.c. of cases it restores the normal rhythm of the heart, but the best results are obtained in cases of recent origin and when the symptoms increased with the onset of fibrillation. It is sometimes useful in **auricular flutter**, the normal rhythm being restored without the intermediate stage of fibrillation. In majority of cases relapse takes place which requires further use of the drug, but this produces no further beneficial effect. It acts by depressing the cardiac muscle which is more marked in the auricle than in the ventricle so that by reducing the conductivity it lengthens the refractory period by 50 p.c. or more and stops the circus movement. It also reduces the frequency of auricular contraction by reducing the excitability of the auricular muscle and thus stops extrasystole, and inducing normal rhythm benefits tachycardia. Its action differs from digitalis where the effect is due to production of partial block in the auriculo-ventricular bundle.

It is rapidly eliminated, the maximum effect being attained in two hours which disappears after twenty-four hours.

According to Hay cases unsuitable for quinidine are :—

(1) Badly damaged hearts with old-standing valvular disease, and more particularly when there is failure of compensation with venous engorgement ; here digitalis is the best drug to use. When compensation is restored it may be given after a week's interval if thought advisable. (2) In patients who suffered severely from angina pectoris, the onset of fibrillation is followed by the cessation of the anginal pain, and it is a question whether one should attempt to restore the normal rhythm. (3) Where there is idiosyncrasy for the drug. (4) Infective endocarditis. (5) Cases with a history of embolism. (6) Heart block.

Cases suitable for quinidine :—

(1) When the fibrillation is of recent origin (best results are obtained in fibrillation of less than six month's duration) and when there is not much dilatation of the heart and no valvular disease. (2) Where the fibrillation is due to, or associated with, an acute infection. (3) When the onset of distress definitely dates from the inception of fibrillation, and it is clear that the abnormal rhythm is the disabling factor. (4) When the fibrillation is associated with exophthalmic goitre, specially where partial thyroidectomy has been performed and the fibrillation persists.

Untoward effects.—The use of quinidine is not entirely devoid of danger and sudden death during treatment has been recorded

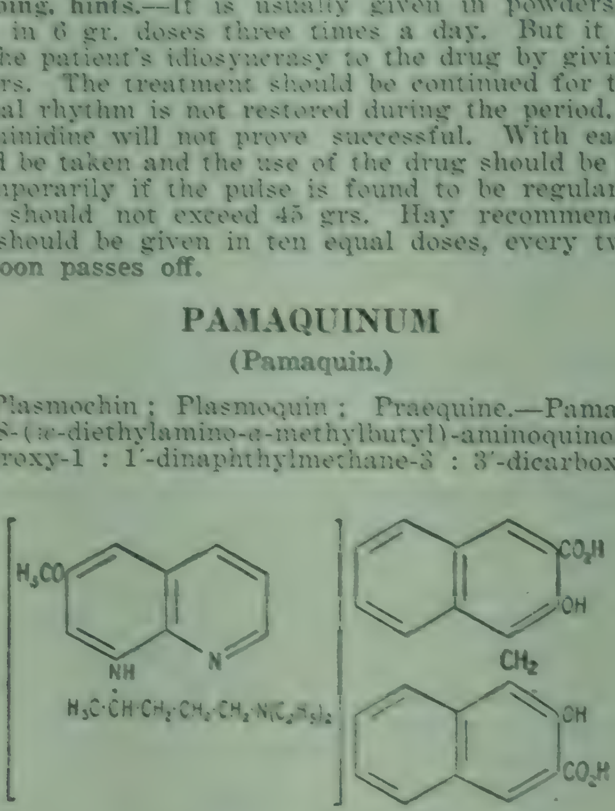
and is possibly due to failure of the ventricular muscle. It frequently causes distressing symptoms, such as headache, nausea, vomiting, diarrhoea, abdominal pain, giddiness, faintness, buzzing in the ears, general distress, a sense of apprehension, palpitation, precordial pain, excessive ventricular rate, orthopnoea, sweating, toxic erythema and urticaria. There may be marked idiosyncrasy resulting in symptoms of respiratory failure and cerebral paralysis when it becomes impossible to push the drug, although it is rather rare when the sensitiveness is so marked as to make treatment impossible. Slight degree of sensitiveness should not prevent a reasonable trial.

Prescribing hints.—It is usually given in powders, cachets or in capsules in 6 gr. doses three times a day. But it is better to determine the patient's idiosyncrasy to the drug by giving an initial dose of 3 grs. The treatment should be continued for ten days and if the normal rhythm is not restored during the period, the chances are that quinidine will not prove successful. With each dose the pulse should be taken and the use of the drug should be discontinued at least temporarily if the pulse is found to be regular. The total daily dose should not exceed 45 grs. Hay recommends that the daily dose should be given in ten equal doses, every two hours, as its action soon passes off.

PAMAQUINUM

(Pamaquin.)

Syn.—Plasmochin; Plasmoquin; Praequine.—Pamaquin is the 6-methoxy-8-(ω-diethylamino-α-methylbutyl)-aminoquinoline salt of 2 : 2′-dihydroxy-1 : 1′-dinaphthylmethane-3 : 3′-dicarboxylic acid.



Characters.—A yellow or orange-yellow powder; odourless; taste, bitter. *Insoluble* in water; soluble in 10 parts of acetone containing 5 p.c. of water.

B. P. Dose.—1/6 to 1/3 gr. or 10 to 20 mg.

Action and Uses

Pamaquin is a synthetic product introduced as a remedy for malaria. It is readily absorbed from the gastro-intestinal tract and slowly excreted by the kidneys. It is effective in benign tertian and quartan malaria, destroying all forms of *P. vivax* and *P. malariae*, in doses of 0.06 grm. (1 gr.) to 0.1 grm. (1½ grs.) daily. But when used in these doses the toxic symptoms often appear. It however destroys the gametocytes of *P. falciparum* in the peripheral blood, therefore this remedy is of great value as a prophylactic, as it prevents the development of the *crescents*

in the mosquito host ; and for this purpose very small doses (20 mg. or 1/3 gr.) twice a week are given. But the onset of crescents in the peripheral blood is not prevented or retarded even by larger doses when given during the acute stage. Its use should therefore be deferred until the acute stage of the disease has been overcome by either quinine, proguanil or mepacrine.

Whereas quinine and mepacrine act on the erythrocytic phase, pamaquin acts on the tissue phase of the malaria parasite. Since the daily dose for this purpose is 80 mg. (1¼ gr.) of the base which is toxic it cannot be used. It is used in selected recurrent cases of malaria to prevent relapses. Being toxic its use in the routine treatment of acute attacks has been given up. When given simultaneously with mepacrine it may produce gastro-intestinal and other nervous symptoms. Even doses of 20 mg. (1/3 gr.) daily if prolonged for ten or more days may cause toxic symptoms. Quinine and pamaquin are less toxic and are of great value in preventing relapses. The best method is to use pamaquin 1/6 gr. (10 mg.) with quinine sulphate 2 grs. three times daily for one week. To prevent relapse, when due to benign tertian, the following method is recommended in the Indian army, *viz.*, quinine sulphate or bihydrochloride 10 grs. three times a day along with 10 mg. (1/6 gr.) pamaquin twice daily after food, for ten days.

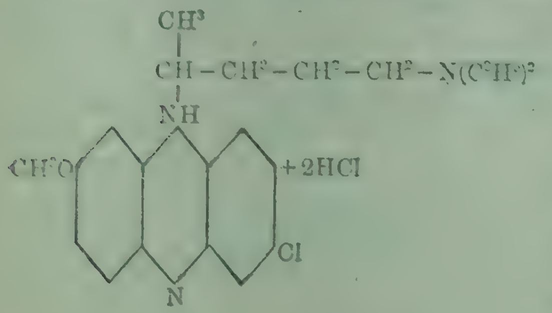
A mass treatment with small doses of pamaquin has been employed in many places as an *antimalarial measure*, but the success depends upon the extent to which the group is under control. Anti-mosquito measure will also be necessary, for though the drug will render the gametocyte carrier incapable of infecting mosquitoes, it will be almost impossible to treat every carrier in a particular place. Combined with antilarval measures it has given remarkable results in many tea states in Southern India, but this treatment alone will be hopeless in an uncontrolled civil population.

Toxic action.—The symptoms may arise with startling suddenness, but as a rule they are less abrupt. Epigastric pain, nausea, cyanosis, fatigue, profuse perspiration, and cardiac troubles accompanied by attacks of vertigo and fainting are often seen. If it is continued, cyanosis spreads, the temperature rises, and an attack resembling black-water fever develops accompanied by destruction of red-blood cells, haemolytic jaundice and black urine containing methaemoglobin. Even in this stage recovery takes place if the drug is stopped and the patient treated with injections of glucose and adrenaline. The symptoms of poisoning appear in those whose liver is already damaged, but some patients are specially susceptible to it.

MEPACRINAE HYDROCHLORIDUM

(Mepacr. Hydrochlor.)

Syn.—Atebrin : Quinacrine ; Erion.—Mepacrine Hydrochloride is the dihydrochloride of 2-chloro-5- (*w*-diethylamino-*a*-methylbutylamino)-7-methoxyacridine. It contains not less than 99 p.c. of $C_{23}H_{30}ON_3Cl,2HCl,2H_2O$.



Characters.—A bright yellow, crystalline powder ; odourless ; taste, bitter. *Soluble* in about 40 parts of water giving a clear yellow solution.

B. P. Dose.—*Prophylactic* :—1½ gr. (0.1 grm.) daily. *Therapeutic* :—3 to 8 grs. or 0.2 to 0.5 grm. daily in divided doses.

Official Preparation

1. **Tabellae Mepacrinae Hydrochloridi.—B. P. Dose.**—*Prophylactic* (daily) :—1½ gr. or 0.1 grm. *Therapeutic* (daily in divided doses) :—3 to 8 grs. or 0.2 to 0.5 grm. N. B. If the quantity to be contained in a tablet is not stated, 0.1 grm. (1½ gr.) tablets shall be supplied.

Mepacrinae Methanosulphonas. Syn.—Atebrin Musonate.—Mepacrine Methanesulphonate is dimethanesulphonate of mepacrine.

Characters.—A bright yellow, crystalline solid ; odourless ; taste, bitter. *Soluble* in 3 parts of water and in 36 parts of alcohol (95 p. c.).

B. P. Dose.—1½ to 5 grs. or 0.1 to 0.3 grm. By intramuscular injection.

Official Preparation

1. **Injectio Mepacrinae Methanosulphonatis.—B. P. Dose.**—By intramuscular injection, 1½ to 5 grs. or 0.1 to 0.3 grm.

Action and Uses

Mepacrine is absorbed rapidly and is detected in the urine within 15 to 30 minutes after a single dose of 0.3 grm. (5 grs.). Its greatest concentration occurs in the urine during the first 24 hours. It is an exceptionally powerful drug and destroys the asexual forms of all the types of malaria parasites. The crescents of the malignant tertian are however not affected at all. The trophozoites of *P. vivax* are eradicated by a concentration of 30 microgram per litre of plasma for four days and for *P. falciparum*, 50 microgram per litre for six days. Its effect on human malaria resembles that of quinine, *i.e.* it destroys all forms of benign tertian and quartan parasites. Therefore in the treatment of these two varieties of malaria, the choice between them must be decided on other considerations than those of immediate therapeutic efficacy. Some cases of quartan are resistant to quinine while others are to mepacrine. Therefore when one drug fails, the other should be tried. In cases of malignant malaria with severe vomiting or other complications which prevent oral administration, mepacrine can be given *intramuscularly*. But the best plan is to give one or two intravenous injections of quinine, followed by oral use of mepacrine.

The usual method of treatment is to give 1½ grs. three

times a day for five days with a saline purgative in the morning. Treatment recommended for Indian troops is mepacrine two tablets at a time three times a day after meals for two days, and one tablet (1½ gr.) at a time three times a day for five days. For prophylaxis a dose of 0.1 grm. (1½ gr.) daily for six days weekly or 0.4 grm. (6 grs.) twice a week after meals is used. With 0.1 grm. six times weekly, the average plasma level is 22 microgram per litre. The suppressive therapy should be continued for four weeks for *P. falciparum.*

It is a drug of choice when there is idiosyncrasy to quinine and in cases of **pregnancy.** Although recommended in black-water fever it should be used with caution in view of several recorded cases of methaemoglobinuria.

It is also useful in **giardia infection** of the intestine in 1½ gr. (0.1 grm.) doses three times a day for five days. The dose for infants is 1/5th of the tablet.

It is excreted slowly and has been found in the urine even eight or nine days after the expiry of the seven-day course. A portion is accumulated in the cells of the liver and spleen. Its presence in the urine is detected by adding sulphuric acid and heating, when a characteristic yellow colour forms, best seen by looking down the test tube.

Mepacrine methanesulphonate is used for intramuscular injection dissolved in 3 mils of sterile distilled water before injection. For intravenous injection the single dose of 0.1 grm. (1½ grs.) should not be exceeded. As the margin of safety is low this route should be used only in emergency.

Toxic action.—Toxicity though low is common when the dose is large. Gastro-intestinal symptoms, *e.g.* vomiting with excessive perspiration and severe pain in the abdomen are commonly observed. Yellow staining of the skin with enlarged and tender liver. The yellow colouration is associated with defective functioning of the liver and kidneys. Methaemoglobinuria has also been reported. Fatty degeneration of the liver and kidneys in dogs and cats was recorded by De Mello. A few cases with mental symptoms, *viz.*, delirium, hallucination, have been recorded.

PROGUANILI HYDROCHLORIDUM

(Proguan. Hydrochlor.)

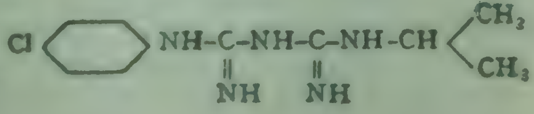
Syn.—Paludrine ; Chlorguanide.

Source and characters.—Proguanil Hydrochloride is the hydrochloride of N-*p*-chlorophenyl-N-*iso*propyldiguanide. A white crystalline powder ; odourless ; taste, bitter. *Soluble* in 110 parts of water ; more soluble in hot water ; soluble in 37 parts of alcohol (95 p.c.) ; almost insoluble in chloroform and in solvent ether.

B. P. Dose.—1½ to 6 gr. or 0.1 to 0.4 grm. daily.

OFFICIAL PREPARATION

1. **Tabellae Proguanili Hydrochloridi.**—B. P. Dose.—1½ to 6 gr. or 0.1 to 0.4 grm. daily. N. B. If the quantity to be contained in a tablet is not stated, 0.1 grm. shall be supplied.



Pharmacology

Proguanil is a synthetic antimalarial remedy belonging to a class of chemical compounds not previously known to have antimalarial property. It attacks the parasites of *P. falciparum* both in their erythrocytic as also exo-erythrocytic stage (tissue phase).

Mechanism of action.—It has been suggested that proguanil acts by a mechanism of substrate competition by interfering with the porphyrin metabolism of enzyme systems of the malaria parasite. It forms a complex with copper having similar structure to the naturally occurring porphyrin pigments and might thus compete with them at some stage of their metabolism in the parasite. Others hold that by itself proguanil is not active but becomes modified by the liver into a new compound which is a powerful plasmodicidal.

Absorption and clearance.—Administered by the mouth proguanil is rapidly and almost completely absorbed, the peak levels are reached within four hours after administration. The concentration in the red blood corpuscles is about four times than that in the blood plasma. A concentration of 0.01 to 0.1 mg. per 100 mils of blood will suppress effectively all forms of human malaria. It is concentrated specially in the liver, spleen, lungs and kidneys. Of the total dose administered about 40 to 60 p.c. is excreted by the kidneys and about 10 p.c. by the faeces.

Drug resistance.—It has been observed that some strains of *P. falciparum* and ordinary strains of *P. vivax* exhibit a degree of resistance and this resistance can be transferred through mosquitoes.

Toxicity.—Even comparatively large doses rarely produce any toxic side-effects. In a small proportion of cases vomiting and epigastric discomfort may occur which may be prevented by taking the drug with a glass of water and are usually apparent during the first few days of the treatment. It does not cause any discolouration of the skin.

Therapeutics

Proguanil like quinine and mepacrine destroys the asexual forms of benign tertian and malignant tertian malaria. A single dose (1 to 3 tablets of $1\frac{1}{2}$ gr. each) will often control the clinical attack in both these infections. In urgent cases it is desirable to use quinine and then follow up with slow acting proguanil. It acts as a true casual prophylactic against malignant tertian malaria, having a definite lethal action on the pre-erythrocytic forms. Though it does not destroy gametocytes, mosquitoes feeding on individuals taking the drug are unable to transmit the infection, *i.e.* renders them non-infective.

In the treatment of malaria with proguanil two lines of action may be adopted, namely, (1) clinical cure, by which is meant reduction of the temperature to normal, and control of the acute attack ; or (2) radical cure.

For *clinical cure*, one tablet of 0.1 grm. or $1\frac{1}{2}$ gr. is usually sufficient to bring the temperature to normal, but it is desirable that three tablets in a single dose (5 grs. or 0.3 grm.) should be given daily for all types of malaria.

For *radical cure*, one tablet (0.1 grm.) three times daily should be given for ten days. It does not cure radically all cases of *P. vivax* infection, and relapses do occur in a certain percentage of cases.

It has been observed that a dose of 0.1 grm. ($1\frac{1}{2}$ gr.) twice weekly or even daily, after an acute attack has been controlled, will prevent relapses. It is possible that by continued suppression the persistent forms of the parasite in benign tertian malaria will be ultimately eradicated.

Clinical prophylaxis.—By this is meant inhibition of the development of the parasite to such a degree that malarial symptoms will not appear. For this one tablet (0.1 grm.) once a week will be found satisfactory in some cases, but in others it may be necessary to administer daily or twice weekly. When taken twice weekly it will not only suppress relapses but will produce causal prophylaxis against malignant tertian malaria.

As regards the prevention of relapse, proguanil possesses little if any advantage over other antimalarial drugs. Since, however, the occurrence of a relapse can be prevented by administering one tablet (0.1 grm.) of the drug daily without any ill-effect to the patient, there seems no reason why this should not be continued until the infection has died out completely.

Administration.—The routine method should be by the mouth. If for any reason, it is not possible to administer orally, because of the presence of vomiting and in cases of pernicious type where immediate action is necessary, it should be administered slowly by the *intravenous route*. For this purpose Paludrine Lactate in 5 p.c. aqueous solution containing 0.1 grm. in 2 c.c. ampoules should be used. The solution should not be diluted with normal saline solution which forms a precipitate.

Chloroquine. (SN 7618). (Not official).—7-chloro-4-(4-diethylamino-1-methylbutylamino) quinoline.—Chloroquine is a quinoline derivative of low toxicity and has been found to be effective against erythrocytic forms of *Plasmodium vivax* and *P. falciparum*, both as a suppressive drug and also as a curative agent in acute attacks.

It is absorbed rapidly and almost completely, only about 10 to 20 p.c. being excreted in the urine unchanged. It concentrates in the liver, spleen, kidneys and lungs as also in the leucocytes. A concentration of 10 microgram per litre of blood is essential to stop asexual cycle. Therapeutic blood levels develop within a few hours and remain for a week. It has been found to be three times more active than mepacrine in these infections. It has however no effect on the exo-erythrocytic (tissue phase) stage of the parasite. It

does not prevent relapse in benign tertian infection even in doses many times than are required in an acute attack, nor has it any effect as a prophylactic. Since its concentration in the liver may be 500 to 1500 times than that in the blood plasma and since it has some amoebicidal action, it has been used in amoebic infection of the liver. As it is completely absorbed from the gut where its concentration is low its value in intestinal amoebiasis is doubtful.

It is generally believed that in benign tertian infection chloroquine is as good as mepacrine or quinine in the control of all symptoms and superior to one or the other in the control of some.

The drug is available as **diphosphate** containing 62 p.c. of the base.

Certain toxic symptoms have been observed after doses adequate for treatment of acute attacks. They are mild transient headache, visual disturbances, pruritus and gastro-intestinal troubles. It is one-third toxic as pamaquin.

Dose.—*For suppression* :—0.25 grm. or 4 grs. once a week on the same day.

For treatment.—Intial dose, 0.6 grm. or 10 grs. followed by 0.3 grm. after 6 to 8 hours, and a single dose of 0.3 grm. on each of two consecutive days. This will irradicate *P. falciparum* infection and terminate an acute attack of *P. vivax* infection.

Pentaquine. (SN 13276). (Not official).—Pentaquine is also a quinoline derivative. It is rapidly absorbed from the gastro-intestinal tract. Plasma levels are quickly attained but declines to zero within 24 hours after it is stopped. The levels can be maintained if administered every four hours night and day. Like pamaquin it acts on exo-erythrocytic cycle. It is however more toxic, the toxicity being qualitatively the same and quantitatively about one-half to three-fourths that of pamaquin. This precludes its use as a prophylactic for prolonged period.

Severe gastro-intestinal trouble, methaemoglobinaemia, haemolytic anaemia, haemoglobinuria and liver damage may occur if the dosage is not carefully restricted.

Dose of 60 mg. or 1 gr. of the base (equivalent to 80 mg. or 1⅓ gr. of diphosphate) and 2 grm. (30 grs.) quinine administered concurrently in divided doses every four hours for 14 days is sufficient to produce radical cure of *P. vivax* infections. This daily dose should not be exceeded. It should be administered only under close supervision. Its toxicity and safe therapeutic dose for children have yet to be determined before it can be widely used.

Camoquin (SN 1075). (Not official).—7-chloro-4-(3-hydroxy-4-diethylamino-methyl-anilino) quinoline dihydrate.—Camoquin is a quinoline derivative having marked parasiticidal action against all forms of malaria in the erythrocytic stage. It has no effect against exo-erythrocytic stage (tissue phase) nor against the sporozoites. It is rapidly absorbed from the gastro-intestinal tract but is excreted very slowly.

It is relatively non-toxic in therapeutic doses. As it is a very recent addition to the antimalarial drugs an extensive clinical trial is necessary before it can be declared as a non-toxic drug as well as before an effective dosage schedule can be laid down.

It is available in tablets as dihydrochloride dihydrate containing 0.2 grm. base.

Dose.—*For suppression* :—0.2 grm. (3 gr.) once a week or 0.6 grm. (10 gr.) every two weeks taken as a single dose.

For treatment.—A single dose of 0.6 grm. or 0.2 grm. twice a day on the first day followed by 0.1 grm. twice daily for the next three days (total 1.0 grm. base).

(Paludrine), Chloroquine and Camoquin in Malaria

	QUININE	MEPACRINE	PAMAQUIN	PROGUANIL	CHLOROQUINE	CAMOQUIN
1. Sporozoites.	No effect.	No effect.	No effect.	No effect.	No effect.	No effect.
2. Exo-erythrocytic forms.	No effect.	No effect.	Effective in toxic doses.	Effective in *P. falciparum.*	No effect.	No effect.
3. Asexual erythrocytic forms.	Effective.	Effective.	Effective in toxic doses.	Effective	Effective.	Effective.
4. Gametocytes.	No effect against falciparum. Slight action against others.	Same as Q.	Effective particularly against falciparum.	No effect; prevents development in mosquito.	Same as Q.	Same as Q.
5. Effective blood concentration.	0.5 mg. per 100 mils.	3 mcg. per 100 mils.	..	0.01 to 0.1 mg. per 100 mils.	1 mcg. per 100 mils.	..
6. Treatment:— (a) Acute clinical attack.	Effective in all types :— 15 grs. daily for 5-7 days; in falciparum infection, 20-30 grs. daily.	Effective in all types :— 1½ gr. t.d.s. for 5 days.	Not effective.	Effective in all types specially against falciparum 300-600 mg. daily for 7 days.	Effective in all types:— 600 mg. (base) stat. 300 mg. after 6-8 hrs., then 300 mg. for next 2 days.	Effective in all types. 600 mg. (base) in a single dose.
(b) Relapse.	Frequent with *P. vivax.*	Less frequent.	Prevented effectively when combined with Q.	Not infrequent.	..	..
(c) Prophylaxis.	Clinical, i.e. suppressive 5 grs. daily.	Clinical, 1½ gr. daily.	True causal but in toxic dose.	True causal against P. falciparum 300 mg. weekly or 100 mg. twice weekly.	Clinical—250 to 300 mg. of the base weekly.	Clinical — 200 mg. weekly.
7. Toxicity.	Cinchonism.	Yellow staining of skin; G. I. irritation; rarely psychosis.	G. I. irritation & methaemoglobinaemia; sometimes haemolytic anaemia.	Non toxic; large doses or in an empty stomach may produce G. I. irritation.	Occasional G. I. irritation & skin rashes.	Rare.
8. Drug resistance.	Nil.	Nil.	Nil.	May develop.	Nil.	Nil.

Class B: Antisyphilitics

For centuries mercury and its salts were used in the treatment of syphilis empirically, since the causative organism of syphilis was not discovered till 1905. Although mercury was used as the only remedy for syphilis, it actually did not cure the disease permanently, for after temporary remission secondary symptoms or tertiary manifestations often appeared. Mercury was used first as fumigation and subsequently by the mouth, and within recent years also as injection. In ancient days, fasting and starvation, bath and fumigations and the violent "salivation cures" often tortured the patient as a result of mercury poisoning.

Following the discovery of *Treponema* (*Spirochaeta*) *pallidum* as the causative organism of syphilis by Schaudinn and Hoffmann in 1905, search was made to find trypanocidal drugs which may be of value in syphilis. In this Ehrlich was guided by the fact that simple organisms like trypanosomes and spirochaetes were more susceptible to the toxic action of organic arsenic compounds than the cells of multicellular organisms. Several drugs which were found to be toxic to trypanosome infection were introduced and tried for the treatment of this disease. Thus atoxyl (pentavalent arsenic compound) which had trypanocidal properties was considered of some value in the treatment of syphilis. Similarly, certain dyes like trypan red and other pentavalent arsenic compounds, chiefly cacodylates, were introduced but these were found to be ineffective in syphilis. In fact pentavalent compounds though of value in trypanosome infection are ineffective in syphilis possibly because these are quickly excreted and do not remain in the body in sufficient concentration to be effective.

After a series of experiments Ehrlich in 1909 discovered the epoch making compound salvarsan (606 or arsenobenzol or arsphenamine) which revolutionised the treatment of syphilis. But being an acid salt, it was necessary to make it neutral with sodium hydroxide and dissolved in a large volume of water before it could be administered intramuscularly or intravenously ; but it often produced toxic symptoms because of the complicated technique required for the preparation of the solution and the large volume of fluid introduced which caused flocculation of the blood. Next advance was the introduction by Ehrlich of neosalvarsan or neoarsphenamine which was not only more easy to administer but far safer though slightly less effective. It was found that although these organic arsenic compounds produced spectacular results inasmuch as the spirochaetes disappeared from the chancre after one or two injections and the Wassermann reaction if positive became negative in most cases, the symptoms re-appeared

after some weeks or months and the symptoms of secondary manifestations began to appear. It was, therefore, necessary to supplement this treatment by slow acting mercury. At first, mercury was administered either by the mouth in the form of Grey powder, generally as Hutchinson's Pill, or as injection, e.g. as Grey oil or calomel injection.

In the year 1916, Sauton and Robert had shown that tartro-bismuthate of sodium was preventive and curative of fowl spirillosis. Subsequently, it has been shown by French physicians to be of value in human syphilis. Since it was realised that the treatment of syphilis either with arsphenamine or neoarsphenamine requires to be supplemented by mercury, introduction of bismuth in 1921 as an antisyphilitic remedy gradually replaced mercury, being less toxic and results more effective. At the present moment, use of mercury in the routine treatment of syphilis has become rare except only in a few cases where the patients are intolerant both to bismuth and arsenic.

In 1934, mapharside (oxophenarsine) was introduced as a substitute for neoarsphenamine and is gradually replacing it as this compound undergoes no chemical change in the body to be effective and does not give rise to unpleasant and dangerous reactions. Standard treatment for syphilis was confined to administration weekly or twice weekly of mapharside (oxophenarsine) for about six weeks followed by the administration of bismuth.

With the introduction of Penicillin in 1944, the treatment now followed is intensive penicillin therapy supplemented by either bismuth or oxophenarsine. In fact, penicillin is now regarded as the drug of choice. In the United States, no additional treatment is recommended. The French venereologists maintain that intramuscular injection of bismuth should be given for two to five years after the initial course of penicillin, while in England bismuth is given by weekly injections for three to six months. Penicillin is the least toxic of all the antisyphilitic remedies so far known, though cases of Herxheimer reaction due to acute activation of syphilitic process have been recorded.

Mention should be made of the use of iodide, first introduced by the Irish physician Wallace in 1836, in the treatment of late stages of secondary syphilis and tertiary manifestations. Iodides have no toxic effect on the spirochaetes, they only dissolve the granulomatous tissues and liberate the parasites to be acted upon by other antisyphilitic remedies like bismuth, mercury or arsenic. In the form of Donovan's solution, which contains mercury, arsenic and iodide, it was largely used. If the modern intensive treatment with arsenic and bismuth, or with penicillin, alone or in combination, actually cures syphilis in

the early stages, one is justified in expecting that eventually late manifestations will not occur and the use of iodides will not be necessary.

HYDRARGYRUM

Mercury. (Hydrarg.)

Syn.—Quicksilver.

Source.—A liquid metal obtained from native mercuric sulphide.

Characters.—A shining, silvery-white heavy liquid, divisible into globules. Extremely mobile. *Soluble* in nitric acid and in boiling sulphuric acid.

Official Preparations

1. **Hydrargyrum cum Creta.** *Syn.—Grey Powder.*—33 p.c. mercury. A greyish blue powder. **B. P. Dose.—1 to 5 grs. or 60 to 300 mg.**
   (*a*) **Tabellae Hydrargyri cum Creta.** *Syn.—Tablets of Grey Powder.*—**B. P. Dose.—1 to 5 grs. or 60 to 300 mg.** N. B. When the quantity to be contained in a tablet is not stated, 1 gr. tablets shall be supplied.
2. **Pilula Hydrargyri.** *Syn.—Blue Pill ; Mercury Pill.*—33 p.c. mercury. **B. P. Dose.—4 to 8 grs. or 0.25 to 0.5 grm.**
3. **Unguentum Hydrargyri.** *Syn.—Blue Ointment.*—30 p.c. mercury.
4. **Unguentum Hydrargyri Dilutum.**—Contains 10 p. c. of mercury.*
5. **Unguentum Hydrargyri Compositum.** *Syn.—Scott's Ointment or Dressing ; Compound Mercury Ointment.*—Contains 12 p.c. mercury.
6. **Unguentum Hydrargyri Nitratis Forte.** *Syn.—Ung. Hydrargyri Nitratis ; Citrine Ointment.*—Contains 6.7 p.c. mercury.
7. **Unguentum Hydrargyri Nitratis Dilutum.** *Syn.—Diluted Mercuric Nitrate Ointment.*—20 p.c. of the strong ointment of mercuric nitrate, or 1.34 p.c. of mercury.

Non-official Preparation

1. **Pilulae Hydrargyri cum Creta et Opii, B. P. C.** *Syn.—Hutchinson's Pill.*—Grey powder, 12 grs. ; Dover's powder, 12 grs.; compound powder of acacia, 1 gr.; syrup of liquid glucose, *q. s.* for 12 pills. *Dose.*—1 pill.

Hydrargyrum Oleatum. (Hydrarg. Oleat.).

Oleated Mercury is a light yellowish unctuous substance obtained by triturating yellow mercuric oxide 20 grms., liquid paraffin 5 grms., and oleic acid 75 grms. Heat to 50°C. Contains equivalent of 20 p. c. of yellow mercuric oxide.

Official Preparation

1. **Unguentum Hydrargyri Oleati.—25 p. c.**

Hydrargyri Oxidum Flavum. (Hydrarg. Oxid. Flav.).

Yellow Mercuric Oxide is an orange-yellow, amorphous powder ; obtained by the interaction of aqueous solution of mercuric chloride and sodium hydroxide. *Insoluble* in water. Contains not less than 99.3 p. c. of pure mercuric oxide.
Enters into.—Hydrargyrum Oleatum, Ung. Hydrargyri Oleati.

Official Preparations

1. **Oculentum Hydrargyri Oxidi.**—1 p. c. yellow mercuric oxide.
2. **Oculentum Atropinae cum Hydrargyri Oxido.**—Atropine 0.125 p. c. ; yellow mercuric cxide 1 p. c.

Hydrargyri Perchloridum. (Hydrarg. Perchlor.). $HgCl_2$. **Syn.**—Corrosive Sublimate ; Perchloride of Mercury.—Mercuric Chloride is obtained by the direct combination of mercury and chlorine. Contains not less than 99.5 p.c. of $HgCl_2$.

Characters.—Heavy, colourless or white, rhombic crystalline masses, or a white crystalline powder. When heated, it fuses to a colourless liquid, which on further heat volatilises as a dense white cloud. *Soluble* in 18 parts of water, in 4 parts of alcohol (90 p. c.), in solvent ether, and in glycerin.
Incompatibles.—Alkalies and their carbonates, potassium iodide, lime water, tartar emetic, silver nitrate, albumin, lead acetate, soaps, and vegetable astringents.

B. P. Dose.—1/32 to 1/16 gr. or 2 to 4 mg.

*Note.—When 'Mercury Ointment', or 'Blue Ointment' is prescribed or demanded, Dilute Ointment of Mercury shall be supplied, unless on enquiry it is ascertained that Ointment of Mercury is required.

Official Preparation

1. **Liquor Hydrargyri Perchloridi.**—1/16 gr. in 60 ms. or 0.1 per cent. **B. P. Dose.**—30 to 60 ms. or 2 to 4 mils.

Hydrargyri Subchloridum. (Hydrarg. Subchlor.). HgCl. Syn.—Calomel ; Hydrargyri Chloridum Mite, U.S.P. ; Subchloride of Mercury.—Mercurous Chloride is a salt obtained as a sublimate when a mixture of mercurous sulphate and sodium chloride is heated.

Characters.—A dull white, heavy, nearly tasteless powder. *Solubility.*—Insoluble in water, in alcohol (90 p.c.), in solvent ether. Volatilises when heated.

B. P. Dose.—1/2 to 3 grs. or 30 to 200 mg.

Official Preparations

1. **Tabellae Hydrargyri Subchloridi.** *Syn.—Tablets of Calomel : Tablets of Subchloride of Mercury.*—**B. P. Dose.—1/2 to 3 grs. or 30 to 200 mg.** N. B. If the quantity to be contained in a tablet is not stated, 1 gr. tablets shall be supplied.
2. **Unguentum Hydrargyri Subchloridi.** *Syn.—Calomel Ointment.*—20 p. c. calomel.

Non-official Preparation

1. **Injectio Hydrargyri Subchloridi.** *Syn.—Calomel Injection.*—Contains 1 gr. calomel in 20 ms. *Dose.*—10 to 20 ms. or 0.6 to 1.2 mils. by intramuscular injection.

Hydrargyrum Ammoniatum. (Hydrarg. Ammon.). NH_2HgCl. Syn.—White Precipitate.—Ammoniated Mercury may be obtained by the interaction of ammonia and perchloride of mercury. A white, odourless powder. *Insoluble* in water, in alcohol (90 p.c.), and in solvent ether.

Official Preparation

1. **Unguentum Hydrargyri Ammoniati.** *Syn.—White Precipitate Ointment.*—Ammoniated mercury 2.5 p. c.

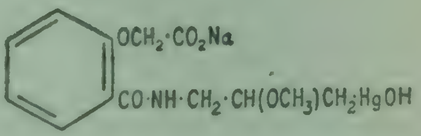
Hydrargyri Oxycyanidum. (Hydrarg. Oxycyanid.).—Mercuric Oxycyanide is prepared by the interaction of mercuric oxide and excess of mercuric cyanide in the presence of water. Contains from 14.5 to 16.5 p.c. of HgO, and 83.5 to 85.5 p.c. $Hg(CN)_2$.

Characters.—A white crystalline powder. Almost completely *soluble* in 18 parts of water, solution alkaline to litmus.

Phenylhydrargyri Nitras. Syn.—Merfenil.—Phenylmercuric Nitrate is obtained by the interaction of a solution of nitrogen tetroxide in ice-cold chloroform with a solution of diphenyl-mercury in ice-cold chloroform, and crystallisation of the compound from moist alcohol.

Characters.—White, lustrous plates, or a white, crystalline powder ; odourless ; taste, weakly metallic and astringent. Slightly *soluble* in water, soluble in about [illegible] parts of boiling water ; soluble in about 1000 parts of alcohol (95 p. c.) ; more soluble in glycerin and in fixed oil.

Mersalylum. (Mersal.).—Mersalyl is the sodium salt of salicyl-(γ-hydroxymercuri-ß-methoxypropyl)-amide-*O*-acetic acid. Contains 2.5 to 2.8 p.c. of N, and 38.5 to 40.5 p.c. of Hg.



Characters.—A white powder ; odourless ; taste, bitter. Deliquescent. *Soluble* in about 1 part of water, and in about 8 parts of alcohol (95 p.c.) ; insoluble in solvent ether.

Official Preparation

1. **Injectio Mersalyli.** *Syn.—Salyrgan.*—Contains about 3 grs. of mersalyl and about 1½ grs. of theophylline in 30 ms. **B. P. Dose.**—8 to 30 ms. or 0.5 to 2 mils. By intravenous or intramuscular injection.

Hydrargyri Iodidum Rubrum, B.P.C. (Hydrarg. Iod. Rubr.). Syn.—Biniodide of Mercury ; Mercuric Iodide.

Characters.—Red Mercuric Iodide is a scarlet-red powder, obtained by the interaction of aqueous solution of mercuric chloride and potassium iodide. *Solubility.*—Almost insoluble in water, but freely in solution of potassium iodide.

Dose.—1/30 to 1/15 gr. or 2 to 4 mg.

Non-official Preparations

1. **Liquor Arseni et Hydrargyri Iodidi, B.P.C.** *Syn.—Donovan's Solution.*—Contains 1 p.c. of each salt ; or 1/7 gr. of each salt in 15 ms. *Dose.*—5 to 15 ms. or 0.3 to 1 mil.

2. **Hydrargyri Iodidum Viride.** *Syn.—Green Iodide of Mercury ; Protoiodide of Mercury.*—In greenish yellow, odourless and tasteless powder. Insoluble in alcohol, ether and water. *Dose.*—1/6 to 1 gr. or 10 to 60 mg.

3. **Unguentum Hydrargyri Iodidi Rubri, B. P. 1914.**—Mercuric iodide 4 p.c. in benzoinated lard.

Additional Non-official Preparations of Mercury

1. **Novasurol.** *Syn.—Marbaphen.*—A double salt of sodium mercurichlorphenyl oxyacetate with diethylbarbituric acid. Contains 33.9 p. c. of Hg. Valuable in *portal cirrhosis, ascites* and *cardiac oedemas,* when it is more effective than digitalis or purine derivatives. White crystalline odourless powder, soluble in water, with slightly alkaline reaction. A powerful *diuretic.* Contraindicated in acute nephritis and enteritis. *Dose.*—2½ grs. or 0.15 grm. in 10 p. c. solution, intramuscularly or intravenously, once or twice a week.

2. **Neptal.**—*O-Hydroxymercuripropanolamide of carboxyphenoxyacetic acid.* Action similar to mersalyl when given by intramuscular injection. Diuresis begins within two hours of administration. In *nephritis* and *oedema* of cardiac and renal origin, and also in *pleural effusion.* Non-toxic. *Dose.*—0.8 to 1.5 mils intramuscularly daily or on alternate days.

3. **Metaphen.**—4-Nitro-5-hydroxymercuri-0-cresol. Contains about 56 p. c. mercury. Incompatible with acids and alkaloids. Does not precipitate proteins or act on instruments. Used for sterilisation of skin, instruments and hands. More potent than corrosive sublimate. Usual strength is 1 in 5000.

4. **Mercurochrome, B.P.C. "220"** *Syn.—Dibromo-hydroxy-mercuri-fluorescein.*—In iridescent green scales. Soluble in water. Contains 24 to 27 p.c. of mercury. A non-irritating antiseptic, largely used in *genito-urinary practice* in 1 to 2.5 p. c. solution. Said to be valuable in refractory cases of *cystitis, pyelitis,* etc. Used intravenously acts as a *powerful urinary antiseptic* during excretion. A 1/2 to 1 p. c. solution as injection in gonorrhoea. A 2 p. c. solution of acetone-alcohol-water mixture has been advocated for sterilisation of the skin before operation. Use has been suggested in *Bact. coli* infection. 1 p. c. solution in *conjunctivitis, ophthalmia neonatorum* and *blepharitis.* As an internal antiseptic it has been used in *puerperal sepsis, meningitis* and *septicaemia* but the results have been disappointing, the dose being 15 to 20 mils of 1 p. c. solution in freshly distilled water. *Dose.—Intravenously,* 2 to 5 mg. per kilo of body weight in 0.5 p. c. solution.

5. **Thiomersalate, B.P.C. Syn.**—*Merthiolate.*—Contains 49 to 50 p.c. of mercury in organic combination. A cream-coloured, non-hygroscopic crystalline powder. Stable in air but unstable in sunlight ; soluble in water and in alcohol (95 p.c.) (about 1 in 8). It is an active antiseptic, enhances the process of healing. It is also a fungicide. A 0.1 p.c. aqueous solution is used for sterilising the skin. Extensively used as an application to wounds and for irrigating the nose and genito-urinary tract. Usual strength is 1 in 10,000 to 1 in 1000. May be used as ointment, jelly or suppository.

Pharmacology

Externally.—Metallic mercury and its salts are absorbed by the unbroken skin. They enter easily through the hair and sebaceous follicles in combination with the fatty acids of the sebaceous glands and circulate either as oleate or albuminate. On the denuded or mucous surfaces they produce the following definite actions :—(1) All mercurials are **antiseptics** and **disinfectants** more specially the corrosive sublimate, since it dissociates easily and gives the maximum concentration of mercuric ions which produce the antiseptic effect. The chloride being soluble in lipoids penetrates into bacteria more easily and is a stronger antiseptic. In dilutions of 1 in 500,000 it prevents the growth of, and in 1 in 25,000 kills, ordinary bacilli. The ammoniate, nitrate, oleate and oxide destroy animal parasites, and are valuable **parasiticides.** (2) Weak solutions of corrosive sublimate (¼ to ½ gr. in 1 oz.), mercurous and many mercuric ointments are antiphlogis-

tic, astringent, stimulant and resolvent. (3) Stronger solutions of the acid nitrate and the perchloride cause inflammation and the concentrated ones sloughing. Phenylmercuric nitrate is a valuable bactericide and fungicide, and about 78 p.c. more active than mercuric chloride, against gram-positive cocci and 64 times as active against fungi.

The usefulness of mercurial salts as germicides is limited. They are precipitated by proteins, they are irritants and have an injurious effect on tissue, and are poisonous when absorbed. It is customary to add some sodium or ammonium chloride to prevent precipitation and to reduce their irritant effect. These form double salts which are less dissociated and therefore less active. Hydrochloric acid and tartaric acid are also used for the same object.

The bactericidal power of mercurials depends upon the concentration used, and whereas they act rapidly in high concentrations they require longer time in dilute solutions. Thus while corrosive sublimate kills typhoid bacillus with a dilution of 1 in 100,000 in 24 hours, it takes 22 minutes with 1 in 20,000, and 2½ minutes with 1 in 1000. Its action is probably due to adsorption, consequently sufficient time must be allowed to enable the drug to penetrate into the bacteria before they are killed.

Internally. **Gastro-intestinal tract.**—Mercurial salts affect the mouth, gums and salivary glands, causing **salivation** and **stomatitis.** This is not the result of direct local action but takes place during the process of excretion by the salivary glands, for it occurs whether mercury is given by the mouth, subcutaneously or as inunction, and since the saliva contains the metal, it has a metallic taste. Salivation is reflex from irritation caused by the metal and is an important and earliest symptom of excessive therapeutic use and of chronic poisoning and is checked by atropine.

Most of the preparations of mercury pass through the stomach unchanged and rarely cause any symptoms of irritation like nausea or vomiting, although taken in large doses, as in cases of acute poisoning, there is inflammation, congestion, haemorrhage and necrosis. In the intestine they form some compound with albumin. But only a small portion of calomel enters into this combination, as quite a large portion of it can be recovered from the stool in an inorganic form. In the duodenum and upper part of the small intestine, insoluble mercury, such as grey powder, blue pill and calomel, irritates the intestines to increased peristalsis beginning in the duodenum and extending through the whole length of the gut and diminishes the absorption of fluid. As a result of this action

the contents are hurried down so rapidly that the bile is not reabsorbed as happens normally, consequently the stools are dark green (calomel motions). X-ray examinations have shown that generally both the small and large intestines are stimulated. Mercurials are therefore **purgatives** and takes about 8 to 10 hours to act. But the soluble preparations, or those salts which become soluble in the stomach, are too irritant to be used as such. The stools are usually soft and there is no pain or straining. Some complain of nausea and vomiting. The purgative action is greatly helped by salines given a few hours later. If the dose is insufficient, or if it fails to produce purgation, or sometimes from idiosyncrasy, mercury may be absorbed producing constitutional symptoms, but it is afterwards re-excreted into the bowels as sulphide.

Mercurials are often credited with some disinfectant action in the intestine. They limit decomposition of food, and retard putrefactive changes in the duodenum and intestine, and check flatulence. The disinfectant action if any is very slight and possibly is the result of the purgative action which removes the decomposing faecal mass.

Liver.—Mercurials do not increase the amount of bile formed in the liver, although some bile appears in the stool. They aid excretion of bile already formed and act as **cholagogues** (formerly called indirect cholagogues). The green calomel stools have been ascribed to the antiseptic properties of mercury checking the growth of bacteria in the gut, and so preventing the normal conversion of bile pigments into stercobilin.

Blood and circulation.—Mercury has very little direct effect on the heart and vessels and the changes observed in the pulse in acute poisoning are due to shock. In chronic poisoning they are the result of cachexia and malnutrition.

Kidneys.—Calomel, or sometimes blue pill, occasionally acts as a **diuretic,** specially in the presence of dropsy. But mersalyl and novasurol are more efficacious than other mercurial salts. They cause profuse diuresis even in normal individuals, and act directly on the kidneys and diminish reabsorption of fluids, while theophylline increases glomerular filtration. Diuresis starts within 6 to 8 hours. When purging follows the use of mercurials less diuretic effect is observed. Since mercury is a protoplasmic poison and is concentrated in the kidney, large doses produce acute nephritis and necrosis of the epithelium of the tubules, congestion and acute inflammation of the glomerulus. These effects are more common with soluble preparations than with insoluble salts as they do not accumulate in sufficient concentration in the blood to produce them. Calomel, or blue pill is often used in

combination with digitalis and squill in the form of Guy's pill (*see* page 285).

Absorption and clearance.—Mercurials are freely absorbed from all surfaces, and after absorption they disappear rapidly from the blood and are deposited in the different organs, chiefly the kidneys, the intestinal walls, and the liver, probably in the form of albuminate. From these depots mercury may be mobilised for several months even after the stoppage of the drug. It begins to be excreted within a few hours of its administration, and may last for several days after a single dose. The organic compounds are eliminated mainly by the kidneys, while the inorganic compounds by the faeces. The elimination is very slow. Therapeutic administration does not as a rule produce an excretion of more than 10 mg. of mercury daily by the kidneys. Whenever the daily excretion is above this, the kidneys suffer injury. The concentration of mercury in the kidneys is higher than in the blood. It is also excreted by the saliva, sweat, milk, gastric juice and bile, but a large portion is reabsorbed from the intestine which makes the quantity excreted in the faeces variable. It has been traced to the foetus through the placental circulation.

Specific action.—Mercury is specific in syphilis, specially in the primary and secondary stages. This is due to its action as a parasiticide for *Spirochaeta* (*Treponema*) *pallida*, for mercury in 1 in 20,000 destroys spirochaeta in test tubes. It is not possible to estimate the exact amount present in the tissues, but probably it acts in very great dilutions. Possibly the maximum concentration in the blood is far too low for any direct effect and it is probable that some compound is formed in the body which acts in very low concentration and exerts a slow toxic effect on the parasites.

Toleration.—Age, sex, and idiosyncrasy greatly modify the action of mercurials. Children as a rule bear mercury better than adults, and males better than females. Patients suffering from granular kidneys, scrofula and scurvy are specially susceptible to this drug. Some are very susceptible to it so that a very small dose may cause salivation. Pregnancy is no bar to the administration of mercury.

Acute toxic action.—This is generally due to accidental or suicidal swallowing of tablets or solutions of perchloride, and has been known to follow the retention of strong solution used as uterine or vaginal douches. If a strong solution is taken there is local corrosion of the mouth, oesophagus and stomach with abdominal pain, vomiting, purging and the passage of serous or bloody stools ; salivation, metallic taste, burning and an ashy discolouration of the mouth and pharynx. Congestion of the stomach and small haemorrhages, hyperaemia, redness and swelling of the mucous membrane, developing into necrotic surface and ulcers along the folds are observed chiefly in the caecum and colon, the small intestine almost entirely escaping. Mercurial stomatitis develops within 24 hours.

The urine becomes albuminous and bloody with casts. Very soon anuria follows with delirium, coma, collapse and death. Very little effect is observed on the nervous system and intellect remains clear.

Treatment.—White of several eggs should be given immediately so as to form a non-corrosive albuminate, followed by immediate lavage of the stomach. After this a pint of milk may be introduced into the stomach which may be removed by lavage if vomiting continues. If the stomach permits, early feeds of milk alternating with potassium bitartrate mixture are useful. Sodium hypophosphite 1 grm., water 10 mils and hydrogen peroxide 0.5 mil per 0.1 grm. of mercuric chloride is more effective (Sollmann). Irrigation of the colon morning and evening is also advisable. This is continued until no mercury is found in the urine on two successive days. The use of alkalies gives the best protection against development of tubal nephritis. If the anuria is not overcome, copious fluid injection may lead to pulmonary oedema. In addition to the usual treatment **BAL** should be administered in 3 mil doses of 10 p.c. solution (*see* page, 533). This is repeated every 4 hours until 4 to 5 such injections have been given. Further injections should be guided by the blood and urinary mercury level.

Chronic toxic action, Hydrargyrism or **Mercurialism.**—This is rare but occurs occasionally either as the result of accident or malpraxis, and among workers in mercury. The first indications of mercurial poisoning are fetor of the breath and soreness of the gums (the medicinal administration of mercury should not go further) soon followed by a disagreeable metallic taste ; swollen, red, spongy gums, bleeding on the least touch ; and increased salivary discharge. The appetite disappears, there is a feeling of weight and discomfort in the stomach, with nausea, colicky pain and diarrhoea. Skin eruption often appears even when given by the mouth, though more common when used as inunction. These symptoms increase, the tongue becomes furred and swollen, the tonsils and pharyngeal glands enlarge, there is swelling and tenderness of the parotid and submaxillary glands, the teeth get loosened, the gums recede and become ulcerated, the saliva gets thick and viscid and pours out of the mouth, fever and depression set in. If the dose is large and long continued these symptoms are aggravated, and end in the falling out of the teeth, ulceration and abscess of the mouth, necrosis of the jaw-bones, great prostration, anaemia, emaciation, repeated haemorrhage, and death.

Protracted exposure to a moderate degree of mercurial vapour produces a different train of symptoms generally known as **mercurial paralysis.** Besides the cachectic symptoms there are muscular tremors, first beginning at the face, then invading the arms and the legs, extreme weakness of the affected muscles ; mental weakness, and functional disturbance of special senses. These tremors increase by attempts at voluntary movement, *i.e.* they are "intention tremors". A condition known as **mercurial erethismus** is characterised by hyper-irritability, restlessness, timidity or shyness and muscular weakness or sleeplessness. Delirium with transitory hallucination may appear.

Metallic mercury vaporises even at the ordinary temperature and may produce poisonous effect even though the evaporating surface be small if the emanations from it continue for any length of time.

THERAPEUTICS

Externally.—As an **antiseptic,** cyanide and perchloride of mercury are used, but the solution of the latter is largely employed for disinfecting purposes, as well as in **surgical** and **obstetric** practice. A solution of oxycyanide

1 in 5,000 to 1 in 10,000 is useful for washing out the bladder and urethra in gonorrhoea. As it does not attack metals the lotion can be used for instruments (1 in 200). A lotion of perchloride (1 in 1000) is used for washing infected rooms, furniture, articles, linen, the surgeon's and gynaecologist's hands, the parts to be operated upon, and for moistening dressing, towels, wool, etc. A lotion (1 in 10,000) may be ordinarily used for washing wounds and ulcers, but the former strength can be advantageously employed if they are foul or of syphilitic origin. A solution of 1 in 5000 is ordinarily used for irrigation of the bladder, vagina and uterus, but its strength requires to be diminished to 1 in 10,000 if used continuously for any length of time. Biniodide spirit lotion* is a valuable antiseptic for the skin and hand.

The following are the disadvantages of perchloride of mercury as a disinfectant :—

(1) It is very poisonous to man.

(2) It corrodes metals.

(3) It combines with albumin—forming an albuminate, on which account it is not good for the disinfection of faeces, unless an acid is also present.

Phenylmercuric nitrate is used as a non-irritant bacteriostatic agent of low toxicity and has the advantage of being slightly affected in the presence of body fluid or by the alkalinity or acidity of the medium. For disinfection of the skin it is used in strengths of 1 in 1500 ; for wound, 1 in 3000 ; and for vaginal douche, 1 in 30,000. As an ointment it has been used as contraceptive.

As a parasiticide.—Citrine, oleate and white precipitate ointments and perchloride lotion (1 to 2 grs. in 1 oz. of water) are employed to destroy the fungus of tinea, such as of ringworm, mentagra and favus ; and animal parasites, such as the various kinds of lice and their nits, and the *Acarus scabei.*

As a remedy for pruritus.—Blue ointment and calomel ointment (60 grs. to 1 oz.) relieve the distressing itching of many skin diseases, such as prurigo, pruritus ani, psoriasis, lichen, pityriasis of the scalp and eczema.

As a stimulant and promoter of absorption.—The liniment and the various ointments, such as oleate, red precipitate, Scott's and red iodide are used for dispersing glandular enlargement and buboes ; and for promoting the absorption of inflammatory products, as in chronic joint disease, chronic peritonitis and periostitis. Red iodide of mercury ointment is a good application for **goitre**, especially if the patient be made to sit in the sun immediately after the application.

* Hydrarg. iod.	grm. 1
Pot. iod.	grm. 1
Alcoh. (70%)	mils 1000

As a specific.—Mercurial ointments are always prescribed for dressing over chancres and other syphilitic sores. A cyanide of mercury lotion (5 to 15 grs. in water 1 oz.) is a good local application to syphilitic sores. They are also of great service in all varieties of skin diseases, originating from syphilis. It should be borne in mind that in all syphilitic sores the local application must be combined with internal administration of anti-syphilitic remedies like penicillin, bismuth or arsenic.

Eye.—Mercury is used in certain diseases of the eye *e.g.* in conjunctivitis, blepharitis and keratitis. For this purpose oculentum hydrargyri oxidi is generally used. Finely powdered calomel is also applied locally in syphilitic and other affections of the eye (phlyctenular ophthalmia). When applied in this way potassium iodide must not be simultaneously administered internally, as it will appear in the lachrymal secretion and then, mixing with the calomel, will produce an iodide of mercury, and violent inflammation of the eye will be the result. A lotion of oxycyanide (1 in 500) is used in ophthalmia neonatorum and 1 in 5000 to 1000 in conjunctivitis.

Internally. **Gastro-intestinal tract.**—Local syphilitic sores in the mouth soon heal under the use of the perchloride mouth-wash. **Vomiting** in infants whether occurring immediately after feeding or at other times is stopped by grey powder in $\frac{1}{12}$ gr. or $\frac{1}{8}$ gr. doses given every two or three hours. **Infantile diarrhoea,** whether acute, subacute or chronic with clay-coloured, offensive, or dark green, or slimy, or curdy, stools, soon yields to small doses of calomel or grey powder. In **infantile cholera,** the vomiting and purging are soon arrested by an hourly dose of grey powder ($\frac{1}{6}$ gr.), while fractional doses of calomel ($\frac{1}{12}$ to $\frac{1}{8}$ gr.) have been found useful in the early treatment of cholera when given every hour till the colour of the stool alters. Cases of obstinate **hiccough** have been checked by small doses of calomel. Blue pill or calomel is given as a **purgative** but it should not be prescribed to habitual opium-eaters, or to a patient under opium treatment, for fear of absorption and constitutional symptoms. Calomel may be prescribed as a single dose at night or in divided doses ($\frac{1}{4}$ to $\frac{1}{2}$ gr.) every half to one hour till $1\frac{1}{2}$ to 2 grs. have been taken. It is always followed by a saline or may be given in combination with compound liquorice powder.

In biliousness or hepatic derangement, a dose of blue pill or calomel at night, followed by a dose of compound senna mixture, or Seidlitz powder or compound liquorice powder next morning, produces excellent results.

Dropsy and ascites.—Calomel given several times a day acts as a diuretic in **cardiac dropsy.** Its efficacy is greatly increased if combined with digitalis and squill, as

in Guy's pill (*see* page 285). It benefits, though temporarily, **ascites** due to **cirrhosis** of the **liver**. It should not be given in renal dropsy. Mersalyl and novasurol are used as diuretics in ascites and in cardiac and other dropsies. They are of great value in congestive failure of the heart and in acute oedema of the lungs. The injections are given intravenously or intramuscularly according to the urgency of the case. An initial dose of 0.5 mil is given to test the tolerance of the patient, and subsequently increased to 2 mils and is given once or twice a week. The effect lasts for eight to ten hours. It acts better when partial acidosis is produced by the administration of ammonium chloride for a few days prior to the injection.* This mixture should be given every six hours and on the fifth and ninth day mersalyl is given by injection. If there is a good diuresis, *i. e.* 90 to 180 ozs. of urine, the injection should be repeated at an interval of one week, and ammonium chloride mixture, two days before, on the day of the injection and the day after, *i.e.* for four days each week. At the same time the total amount of fluid intake in 24 hours should not be more than 40 ozs. Mersalyl is less toxic than novasurol. Since mercury has a special toxic effect on the kidney, these drugs are best used in cardiac dropsies and should not be used in acute and advanced **nephritis.**

Syphilis.—Mercury has been used for centuries in the treatment of syphilis till the introduction of the arsphenamines. Brilliant though the results were with organic arsenic compounds, it was soon realised that the treatment required to be supplemented by the use of mercury. Because of lower toxicity and better therapeutic results the use of mercury has been replaced by bismuth. Whereas the concentration necessary to sterilise the tissue with arsenic is obtained quickly it requires several weeks to obtain the same result with mercury. It is therefore necessary that as soon as the case is diagnosed and before the parasites migrate into more inaccessible parts of the body, one of the arsenic preparations like neoarsphenamine or oxophenarsine should be used and bismuth or mercury used **immediately afterwards.**

Recently penicillin has been used in the treatment of syphilis. The result of intensive penicillin therapy for two weeks has been found to be perhaps as effective, if not more, than prolonged arsenic treatment. In fact opinion is gaining ground that penicillin treatment combined with arsenic or bismuth appears to act synergistically.

By whatever method it is administered mercury tends

* Ammon. chlorid.	grs. 80
Ext. glycyrrh. liq.	ms. 20
Sp. chlorof.	ms. 10
Aqua	ad. oz. 1

to produce cumulative effects, therefore in the treatment of syphilis there must be periods of rest when the patient should not get any mercury.

Mercury is also valuable as a *prophylactic*, for this purpose calomel 33 p. c. with lanoline ; or oxycyanide of mercury 0.66 grm., glycerin 50 mils and water to 500 mils heated in a water bath for one hour, may be applied as inunction into the part exposed. To be effective the application should be made within 4 to 5 hours after exposure. But its thorough application by women is impossible.

Although the use of mercury is not the method of choice in the treatment of early syphilis, it is well to remember that its use becomes necessary when one is face to face with a case intolerant to both arsenic and bismuth. It may be administered by the following routes :-

1. *By the mouth.*—This is by far the most convenient route, but it is rather difficult to administer sufficient mercury on account of its effect on the digestive tract and purgation which causes the absorption to be irregular. Grey powder is the most widely used preparation, and since it is liable to cause diarrhoea and looseness of the bowels, it is customary to combine it with opium in the form of Dover's powder. The mouth must be kept clean during the treatment.

2. *Inunction.*—By rubbing blue ointment, liniment, or oleate of mercury into the skin mercury can be introduced into the system. The inner surface of the thigh or the axilla is a suitable spot for inunction. This method is especially useful for the treatment of young children ; 20 to 60 grs. of blue ointment may be rubbed in nightly or every other night. The site should be varied to avoid local irritation. The advantage of this method is that digestion is not disturbed, but it is dirty and disagreeable and special skill is required to avoid cutaneous irritation. By this method sufficient mercury can be introduced to produce saturation of the system in about two weeks.

3. *Injection.*—For intramuscular injection calomel has been used ; and twelve injections at weekly intervals are usually given deep into the gluteal or lumbar muscles. The advantage of the insoluble preparation is that a large dose of mercury is put in, which usually suffices for a week, and that from these "depots" the mercury continues to be absorbed for some weeks. On the other hand the disadvantages are—accuracy of dosage is impossible, toxic symptoms may continue long after suspending treatment by absorption from these "depots."

Prescribing hints.—As a purgative mercury is usually prescribed in the form of either calomel or blue pill. They may with advantage be used at bedtime to be followed by a saline, black draught, Epsom salts, Glauber's salt, or Seidlitz powder. Grey

powder in fractional doses is a valuable remedy for children's dyspepsia. As a diuretic mercury is given as injections of mersalyl or novasurol.

For external use the oleate is a very useful preparation and is non-irritant. The white precipitate ointment is a valuable antiparasitic and may be used diluted with equal parts of boric ointment. The student should remember that liquor hydrargyri perchloridi is incompatible with alkalies and when combined with carbonate of ammonia it forms an insoluble precipitate of ammoniated mercury, which is less poisonous and can be dispensed suspended with mucilage and a "shake the bottle" label used. With potassium iodide it forms potassium mercuric iodide. If however the carbonate of ammonia be added after this combination no precipitate of ammoniated mercury is formed. With tannic acid or substances containing it, salts of mercury form insoluble tannates.

BISMUTHI CARBONAS

Bismuth Carbonate. (Bism. Carb.)

Syn.—Bismuth Oxycarbonate ; Bismuth Subcarbonate.

Source.—Obtained by the interaction of bismuth nitrate and a soluble carbonate.

Characters.—A white or creamy-white powder ; odourless and tasteless. *Insoluble* in water, completely soluble with effervescence in nitric and hydrochloric acids.

B. P. Dose.—10 to 30 grs. or 0.6 to 2 grms.

Official Preparation

1. **Trochiscus Bismuthi Compositus.**—2½ grs. in each.

Bismuthi Salicylas. (Bism. Salicyl.). **Syn.**—Bismuth Subsalicylate.—Bismuth Salicylate is obtained by the interaction of solutions of bismuth nitrate and sodium salicylate.

Characters.—A white or nearly white, microcrystalline powder ; odourless and tasteless. *Insoluble* in water.

B. P. Dose.—10 to 30 grs. or 0.6 to 2 grms. By intramuscular injection :—1 to 3 grs. or 60 to 200 mg.

Official Preparation

1. **Injectio Bismuthi Salicylatis.**—Contains 2 grs. of bismuth salicylate in 20 ms. **B. P. Dose.**—10 to 20 ms. or 0.6 to 1.2 mils intramuscularly.

Bismuthum Praecipitatum. (Bism. Praecip.).—Precipitated Bismuth is obtained by the reduction of a solution of bismuth trichloride in hydrochloric acid by means of hypophosphorous acid. Contains not less than 98.5 p.c. of metallic bismuth.

Characters.—A dull grey powder. Easily diffusible in water. *Insoluble* in water.

B. P. Dose.—1 to 3 grs. or 60 to 200 mg. intramuscularly.

Official Preparation

1. **Injectio Bismuthi.**—Contains 3 grs. in 15 ms. **B. P. Dose.**—8 to 15 ms. or 0.5 to 1 mil intramuscularly. This is known under the proprietary name of Bismostab.

Bismuthi et Sodii Tartras. (Bism. et Sod. Tart.). **Syn.**—Bismuth Sodium Tartrate ; Sobita.—Sodium Bismuthyltartrate may be obtained by the interaction of bismuth hydroxide and sodium acid tartrate. Contains 35 to 42 p.c. of Bi.

Characters.—A white powder, or slightly yellow scales. *Soluble* in less than 2 part of water.

B. P. Dose.—1 to 3 grs. or 60 to 200 mg. intramuscularly.

Official Preparation

1. **Injectio Bismuthi et Sodii Tartratis.**—**B. P. Dose.**—*By intramuscular injection* 1 to 3 grs. or 60 to 200 mg. N. B. When no strength is stated, a solution containing 1 gr. in 15 ms. shall be dispensed.

Bismuthi Oxychloridum. (Bism. Oxychlor.). **Syn.**—Bismut Subchloride.—Bismuth Oxychloride is basic salt of varying composi tion, obtained by the interaction of solutions of bismuth nitrate an sodium chloride or hydrochloric acid. Contains 79 to 81 p.c. of B and not less than 12.5 p.c. of Cl.

Characters.—A white or nearly white, amorphous or finely crystalline powder odourles; tasteless. Stable in air. *Insoluble* in water, soluble in dilute hydr chloric acid.

B. P. Dose.—10 to 30 grs. or 0.6 to 2 grms. By intramuscular injection :— **to 3 grs. or 60 to 200 mg.**

Official Preparation

1. **Injectio Bismuthi Oxychloridi.**—Contains 3 grs. of bismuth oxychloride i **30 ms. B. P. Dose.—15 to 30 ms. or 1 to 2 mils intramuscularly.**

Bismuthi Subgallas. Syn.—Bismuth Oxygallate; Basic Bismut Gallate; Dermatol.—Bismuth Subgallate may be prepared by th action of gallic acid on freshly precipitated bismuth hydroxide.

Characters.—A citron-yellow powder; odourless; tasteless; stable in air. *In soluble* **in water, in solvent ether, and in dehydrated alcohol.**

Official Preparation

1. **Suppositoria Bismuthi Subgallatis.**—Contains 5 grs. bismuth subgallate.

Non-official Preparations

1. **Pasta Bismuthi Subnitratis et iodoformi, B. P. C.** *Syn.*—B.I.P.P.—Mix bismuth subnitrate 1, iodoform 2, and stir in liquid paraffin 1 or *q.s.*
2. **Liquor Bismuthi et Ammonii Citratis, B. P. C.**—Bismuth subnitrate, 70 citric acid, 52 : dilute solution of ammonia, *q. s.* ; distilled water, *q. s.* 1000. *Dose.*— **1/2 to 1 dr. or 2 to 4 mils.**
3. **Pulvis Bismuthi Co., B. P. C.**—Bism. carb. 1, calc. carb. 3, mag. carb. pond 3, sod. bicarb. 1. *Dose.*—15 to 60 gr. or 1 to 4 grms.
4. **Bismuth Oxyiodogallate, B.P.C.** *Syn.*—*Airol.*—A greyish-green powder use as a substitute for iodoform, and injected as an emulsion with glycerin (10 p.c.) in *gonorrhoea.*
5. **Bismuthi Subnitras, B.P.C.**—A heavy, white inodorous powder with slightly acid reaction. Insoluble in water. *Dose.*—5 to 20 grs. or 0.3 to 1.2 grms.
6. **Bismuthi Tribromophenas, B.P.C.** *Syn.*—*Xeroform.*—A greenish-yellow powder. Powerful intestinal antiseptic, recommended in *cholera*. Used also as a dusting powder in place of iodoform. *Dose.*—5 to 15 grs. or 0.3 to 1 grm.

Additional Derivatives of Bismuth

1. **Bismuth Arsphenamine Sulphonate.** *Syn.*—*Bismarsen.*—A yellow soluble compound. Arsenic 13 p. c. and Bismuth 24 p. c. Valuable in early syphilis in 0.1 to 0.2 grm. (1½ to 3 grs.) *intramuscularly. Dose.*—0.2 grm. in 1 mil sterile water to which **2** ms. of 2 p.c. solution of butyn has been added. Two injections weekly.
2. **Quininae Iodobismuthus, B.P.C.**—Contains quinine 16.0 to 20.0 p.c., bismuth 21.5 to 24.5 p.c. and iodine 56.0 to 59.0 p.c. *Dose.*—1½ to 5 gr. or 0.1 to 0.3. grm
   - (a) **Injectio Quininae Iodobismuthatis, B.P.C.**—10 p.c. in arachis oil *Dose.*—15 to 45 ms. or 1 to 3 mils by ***subcutaneous*** or ***intramuscular injection.***
3. **Bismosol.**—Potassium sodium bismuthotartrate in aqueous glucose solution 35 p. c. of bismuth. *Dose.*—1 mil of a ten p. c. solution intramuscularly every two days for 20 doses.
4. **Iodobismitol.**—Sodium bismuth iodide and sodium iodide in propylene glycol *Dose.*—16 to 20 injections of 2 mil (corresponding to 0.025 grm. metallic bismuth) every three days intramuscularly.
5. **Sobisminol Mass.**—A complex of sodium bismuthate, tri-isopropanolamine and propylene glycol *Dose.*—2 to 3 capsules (each contains 0.15 grm. or 2½ grs bismuth) orally 3 times a day with plenty of water for 10 to 12 weeks.
6. **Thio-bismol.**—Sodium bismuth thioglycollate. A yellow, granular powder, freely soluble in water. Contains 38 p.c. of bismuth. *Dose.*—0.2 grm. (3 grs.). Three times a week intramuscularly for 3 to 5 weeks.

Pharmacology

Externally.—Bismuth salts have no action on the unbroken skin, but applied to wounds they dry the secretion and form a protective covering and help healing. The ac-

tion is purely mechanical. On the denuded surface they act as sedative, mild astringent and antiseptic.

Internally. **Gastro-intestinal tract.**—Bismuth salts blacken the tongue, have no taste and produce a feeling of roughness in the mouth. In large doses they act as direct sedative to the mucous membrane of the stomach. They act physically by shielding the nerve-terminations from the irritating secretions by forming an adhesive coating on the wall of the stomach and so protect it from the irritation of food and secretions. As a consequence of sedative effect, they act as antiemetics and mild astringents. This sedative and astringent effect extends down to the intestine and bismuth salts produce constipation, the subgallate being more astringent and powerful. They also control fermentation, especially the salicylate, and are therefore intestinal antiseptics. They pass out with the faeces as a sulphide, colouring them leaden black.

Absorption and elimination.—Bismuth salts are not absorbed from the gut and even soluble preparations become insoluble powders and pass through the stomach and intestine unabsorbed as oxychloride in the stomach and as sulphide in the intestine. Very large doses have been given by the mouth for X-ray examination without eliciting any toxic symptoms. The rate of absorption when given intramuscularly is slow and depends upon the site of injection, the dose and on the nature of the preparation used. The exact manner in which it is absorbed is not known, although it is possible that the phagocytic cells may play some important part in this process. Insoluble compounds slowly become soluble by the interaction with the proteins, so that most of the compounds are tissue soluble. Oily suspensions delay these tissue reactions and become encapsulated before they are absorbed, while the water-soluble ones are precipitated and react like insoluble compounds. After intramuscular injection some may be stored in the liver and other organs, but the greater portion is eliminated by the kidneys, liver and the intestine. Minute quantities have been traced to saliva, tears and sweat. It appears in the urine within 18 to 24 hours, and can be detected even after 20 to 30 days.

Kidneys.—Stockton* claims that Bismuth Sodium Tartrate given intramuscularly acts as a powerful **diuretic.** It is in many respects superior to mercurial diuretics, being safe and effective. Its action is less sudden but more prolonged, and acts by mobilising salt in the tissues of the body and bringing it into the blood stream. The **usual dose is 30 mg. (½ gr.).**

Toxic effects.—The earliest symptoms are a disagreeable taste, coated tongue, foul breath and a blue line along the margin of the

* *Archives of Internal Medicine*, 1932, 142.

gums. These are followed by loss of appetite, nausea, vomiting a diarrhoea with stomatitis, nephritis and enteritis. Occipital hea ache, restlessness, mental depression and tingling of the hands fo lowed the use of a certain number of injections of bismogenol (bas bismuth salicylate). The urine contains albumin and casts. Wea ness, slowness and inco-ordinate movements follow and may lead tetanic convulsion. There may be complete paralysis and deat In severe forms of ulcerations of the mouth, cancrum oris ma supervene.

Sometimes serious exfoliative dermatitis and rarely jaundi may appear.

Administration of large doses of subnitrate for radiologic purposes gave rise to symptoms of poisoning due to the formati of nitrite in the large intestine by the reducing action of putrefa tive faecal bacteria. The symptoms were methaemoglobinuria, cya nosis, diarrhoea, asphyxia and death from respiratory failure.

Resnik† reports a case of bismuth poisoning following the us in a fortnight of 5 to 7 ozs. of subnitrate. The chief sympton were a bluish black discolouration of the gums, which were swelle and inflamed; a similar discolouration of the tongue, most marke at the apex of the papillae; a patchy diffuse discolouration of th buccal mucosa; swelling and tenderness of the gland; modera anaemia and basophilic stippling of the red cells, clinical pictu closely resembling lead poisoning. Bismuth was detected in th urine. Recovery followed the withdrawal of the salt.

Treatment.—As a rule the symptoms disappear on stoppage treatment. Attention to oral hygiene and administration of sodiu thiosulphate 15 grs. daily by injection for five days control ging vitis and stomatitis which are very troublesome. Hydrogen pe oxide for washing the mouth and painting the gum with solution iodine are helpful.

THERAPEUTICS

Externally.—As a local sedative, astringent and ant septic bismuth may be applied in the form of powder, lotio or ointment to irritable ulcers, intertrigo, herpes, eczem etc. The subgallate is a non-irritating astringent and i used alone or mixed with boric acid or starch as a dustin powder in place of iodoform. An ointment (10 p.c.) i paraffin basis is used in eczema and burns or in chancroid The suppository is useful in inflamed and bleeding pile Bismuth has been used as bismuth-iodoform-paste (B. P. P.) in the treatment of tubercular sinuses, and fistula It is injected into these and very good results have bee obtained. The chief disadvantage is that both bismut and iodoform may be absorbed and produce toxic symptom but the relative non-toxicity is due to the presence of par ffin which prevents their absorption.

Internally.—As a *gastric protective and sedative* bis muth salts are remarkably efficacious in all irritable an painful gastric disorders, such as catarrh, vomiting, in digestion, gastrodynia, pyrosis and ulcers, simple an malignant. The only drawback to their use is that the cause constipation. As an antacid the carbonate is gene

†*Bull. Johns Hopkins Hospital*, *May*, 1926.

ally combined with magnesium carbonate and bicarbonate of soda (*see* page 77 and 130). They should be given on an empty stomach so as to form a uniform coating over the mucous membrane. If the pain is intense they may be combined with morphine, belladonna, or dilute hydrocyanic acid.

As an *intestinal sedative* and *astringent* bismuth salts are largely employed in all forms of **diarrhoea, acute or chronic**, either in children or adults. The salicylate is a useful remedy for children's diarrhoea due to decomposition of food, because it has the properties of both bismuth and salicylic acid. Occasionally it may with advantage be combined with grey powder. In doses of 15 to 20 grs. the subgallate is valuable in the treatment of ulcerative colitis. Bismuth salts are most effective remedies in **mucous diarrhoea** and **dysentery**, and is often combined with castor oil (*see* page 370). In the last disease they may be given with Dover's powder to check the after diarrhoea.

Syphilis.—Bismuth salts are used in the treatment of syphilis and within recent years have practically replaced mercury being safer and more effective. In doses which can be given intramuscularly safely, bismuth preparations have greater and more rapid therapeutic effect than mercury. Although they may not be so quickly acting as arsenical preparations, but the effects are more permanent than those of arsenic. Small amounts are absorbed and enter the tissues where they possibly act as poisons to the spirochaetes, or at best inhibit their multiplication. Since it is not possible to introduce this drug in sufficient concentration to produce immediate result, the treatment is continued for a prolonged period in maximum tolerated concentration. There is no doubt that the **organic arsenic** compounds are more rapid in their effects and should get the preference in the primary stage of the disease. But all authorities agree that this requires to be supplemented by bismuth. It is of special value in those manifestations of the disease which are resistant to both mercury and arsenic. Since bismuth has been found in the cerebrospinal fluid of treated cases and being neurotropic, favourable results are expected in the syphilis of the central nervous system. The results in general paralysis are disappointing, though it sometimes does good in tabetic crisis.

Lees summarises the value of bismuth in the treatment of syphilis as follows :—(1) It is more rapid in its effects than mercury but not so as the salvarsan group of drugs ; (2) the surface lesions are influenced as rapidly as arsenobenzol but more rapidly than mercury ; (3) combined treatment with bismuth and arsenic is more potent than either given separately, and if the therapeutic doses are not exceeded the treatment has no untoward effect ; (4) metallic bismuth in isotonic glucose solution is free from pain and other side effects, and is better tolerated in this form than either arsenic or

mercury ; (5) this treatment is of special value in cases intoler
to arsenic or mercury ; (6) it is best used as an adjunct to o
treatment and should not be used alone, even in very earliest ca
except in cases showing intolerance to arsenic or mercury.*

Other uses.—In association with the X-ray, bismuth has be
largely used for diagnostic purposes in connection with diseases
the *gastro-intestinal tract*, but its place has now been taken
barium sulphate (*see* page 108), which is less expensive and just
effective.

Prescribing hints.—In the treatment of syphilis bismuth p
parations should be used intramuscularly, the intravenous inject
of the soluble salts is toxic and directly paralyses the heart and c
culation, and is not used ; moreover, it is rapidly excreted. Sub
taneous injection causes too much irritation. The object is to fo
depots of slowly soluble compounds which may then be gradual
and continuously absorbed. It has however the disadvantage
forming local fibrosis, when absorption of the drug from these dep
becomes progressively impaired and finally arrested. Some patien
show several of these nodules. This objection is less when pota
sium bismuth tartrate is used, as this is usually absorbed, or di
appears from the site of injection in 2 to 4 weeks. The soluble pr
parations are more quickly absorbed but are more toxic, while meta
lic bismuth and oxychloride are safe and absorbed at a uniform ra
Injectio bismuthi and injectio bismuthi oxychloridi are suspensio
in glucose and are rapidly absorbed than injectio bismuthi salicyl
tis which is suspension in oil. It is customary to give these inje
tions in doses of 0.2 to 0.24 grm. or 0.1 to 0.2 grm. at intervals
four days to one week. The total amount given in a course vari
from 2 to 3 grms. After ten injections it is necessary to wa
till it is absorbed, generally four weeks, before starting with th
second course. A point midway between the ischial tuberosity an
the posterior superior iliac spine is chosen and sterilised by iodin
The needle is then thrust perpendicularly into the muscle. See th
no blood comes out of the needle before giving the injection.

When giving bismuth by the mouth, remember that the le
soluble preparations allay irritation better than the soluble one
and they are to be preferred when gastric or intestinal irritabili
is a prominent symptom. If they are given in a mixture they shou
be suspended by the compound tragacanth powder, and not by th
mucilage of acacia, as the latter may convert the mixture into a jell
like mass. Again the subnitrate should not be combined with an
alkaline carbonates, for bismuth oxynitrate slowly parts with nitr
acid in water and gives off carbonic acid. Neither should it
mixed with iodides in a mixture as they turn yellow from fr
iodine and from formation of iodide of bismuth. These salts shou
not be used with preparations containing tannin which form insolu
tannate of bismuth.

ARSENI TRIOXIDUM

Arsenic Trioxide. (Arsen. Trioxid.).

Syn.—Arsenic ; White Arsenic ; Acidum Arseniosum. *Sank*
Hind. *Sanko*, Beng.

Source.—Obtained by roasting certain arsenical ores. Co
tains not less than 99.8 p. c. As_2O_3.

Characters.—A heavy, white powder or irregular lumps having a vitreous fr
ture, containing frequently both transparent and opaque varieties. Soluble slow
in 65 parts of water, freely in acidulated water, or solutions of alkali hydroxi
or carbonates ; slightly in alcohol (90 p. c.).

Incompatibles.—Lime water, iron salts, magnesia and astringents.

B. P. Dose.—1/60 to 1/12 gr. or 1 to 5 mg.

* *British Medical Journal*, Aug., 1927.

Official Preparation

1. **Liquor Arsenicalis.** *Syn.—Fowler's Solution.*—Contains 1 p.c. w/v of arsenious trioxide, or about 1/12 gr. in 8 ms. B. P. Dose.—2 to 8 ms. or 0.12 to 0.5 mil.

Arseni Triiodidum. (Arsen. Triiod.). B.P.C. Syn.—Arsenii Iodidum; Arsenious Iodide.

Characters.—Small, orange crystals. *Soluble* in 18 parts of water, in 42 parts of alcohol (90 p.c.), in ether, chloroform and in carbon disulphide.

Dose.—1/16 to 1/4 gr. or 4 to 16 mg.

Non-official Preparations

1. **Ferri Arsenas.**—A tasteless, amorphous greenish powder. *Dose.*—1/16 to 1/4 gr. or 4 to 16 mg.
2. **Sodii Arsenas Anhydrosus.**—A soluble white powder. *Dose.*—1/40 to 1/10 gr. or 1.5 to 6 mg.
3. **Liquor Arseni et Hydrargyri Iodidi,** B.P.C. *Syn.—Donovan's Solution.*—1 p.c. solution. Contains 1/7 gr. of each salt in 15 ms. *Dose.*—5 to 15 ms. or 0.3 to 1 mil.

Pharmacology

Externally.—Arsenic is a local **irritant** acting slowly on the tissues producing inflammation which may even cause sloughing. This irritant action is more marked on the denuded surface or mucous membrane. After prolonged application the cells die, but it is more destructive to pathological tissue than healthy cells.

Internally.—In small therapeutic doses it increases the gastric vascularity and secretion, and thus improves appetite and digestion. In large doses it is a powerful **gastro-intestinal irritant,** and causes severe inflammation of the whole digestive tract. The gastric and intestinal mucous membranes become congested and swollen and even show signs of haemorrhage. These effects are due to paralysis of the capillaries of the splanchnic area which permit the passage of fluid into the tissues more readily than normally, and as a result of this action there is exudation, oedema and increased peristalsis with watery stools which contain shreds of mucus and coagulated exudation forming the so called rice water. The same symptoms are observed when arsenic is administered subcutaneously though only traces of arsenic are found in the stomach.

Blood.—The action of arsenic on the blood is not well understood, although it is used in some forms of anaemia. The improvement may be due, as Stockman has suggested, to some specific effect on some undiscovered toxin or parasite, or as pointed out by Gunn to anti-haemolytic action which protects the red corpuscles from destruction. Arsenic increases the leucoblastic elements of the bone marrow which becomes more vascular, and this may have some share in improving anaemia. Some hold that arsenic sets free some of the blood forming principles by causing destruction of a portion of the patient's liver.

Heart and circulation.—The mammalian heart is little affected, but in poisoning the muscles are directly

depressed. The capillaries dilate enormously and t blood pressure falls. This effect is due to the direct acti of the drug on the capillary walls, specially those of t splanchnic area. Since the pressure falls even when t intestines are tied, it follows that besides the splanchni other vessels are also dilated, the splanchnic vessels, how ever, are more susceptible to the action of arsenic tha those of the rest of the body. The arsenites are mor toxic than the arsenates and the inorganic preparation more than the organic ones.

Metabolism.—In minute doses administered for a lon time arsenic enjoys the reputation of increasing growt and nutrition by checking oxidation. The condition o the skin improves, the bones become longer and more com pact and there is increased vascularity of the bone marrow. It is not clearly understood how these change are brought about since the results of different observer have been different. While improvement in nutrition ha been reported by some observers others like Stockma and Greig observed no change in the growth of animal under prolonged use. Prolonged use lessens the activit of the liver and reduces the formation of glycogen, whic may disappear entirely. The carbohydrate metabolism i stimulated so that a large amount of sugar is assimilate without producing glycosuria. The liver becomes en larged and the pressure on the bile ducts prevents escape o bile into the duodenum, producing jaundice and allowin bile pigments to appear in the urine. There is increase protein breakdown and although the total nitrogen of th urine is not much altered, there is increased amount o urea, ammonia, leucin, tyrosine, etc. Fatty degeneratio of the liver, kidneys, heart and muscles generally i evident. Binz and Schulz explain the action by supposin that it acts as a carrier of oxygen, which it receives an gives up, by transformation of arsenious to arsenic aci and by the reduction of the arsenic into arsenious acid This theory however does not explain all the effects o arsenic.

Nervous system.—Ordinarily no special action on th nervous system is elicited by arsenic since in acute poison ing death takes place from gastro-intestinal irritatio before any nervous symptoms can develop. Sometime paralysis of the extremities appear with disturbances o sensation from central action, although they may be par tially explained by the disturbances of nutrition. I chronic poisoning symptoms of peripheral neuritis develo with limited areas of paralysis.

Skin.—Arsenic has a marked effect on the nutritio of the skin, it improves the complexion and cutaneou nutrition, and increases the subcutaneous fat. It is elim

inated with the sweat and causes itching and eruptions, which may be erythematous, papular, pustular, furuncular, pigmentary or urticarial. In chronic poisoning skin rashes are common and are due to direct action on the skin. These effects may be due either to some specific action produced by the drug upon the epithelium of the skin during excretion, or increase of lymph to the part. The most characteristic action is the darkening of the skin, "*arsenical melanosis*," which may vary from slight pigmentation to a deep brownish-red, and is due to deposition of some organic compound in the deeper layers of the corium.

Toleration.—Long continued use leads to tolerance, so that quantities which would otherwise cause toxic symptoms are taken without any ill-effects. The peasants of Styria take arsenic to improve their complexion and power for work and they can undergo extreme bodily exertion without any respiratory distress. It is not known how this tolerance is established, although it is possible that long continued use may help formation of some antitoxin, or that the body is able to fix it in some non-toxic form. Some hold that absorption is so delayed that acute poisoning does not occur and in support of this view mention that arsenic eaters suffer from the symptoms of poisoning when the drug is administered in solution or hypodermically. It is evident that there is no true tolerance and that the body cells remain susceptible to arsenic. Housman attributes it to increased excretion. He has further shown that the corrosive action of arsenic on the gut is diminished by habituation.

Clearance.—Arsenic is excreted chiefly in the urine and to some extent in the faeces. A small percentage is also excreted in the bile, sweat, saliva, tears and milk. The excretion begins within two to eight hours after administration. It has been found in the hair and epithelial scales and even in the fluid of the blister in patients taking arsenic. Given by the mouth it is excreted by the intestine, while used hypodermically it is eliminated largely by the kidneys. Its elimination is very slow and incomplete and traces may be recovered two or three weeks after stoppage of its use. It is therefore cumulative. Less than 20 p.c. appears in the urine and faeces in the first 24 hours. The arsenic retained is distributed throughout the body, a considerable amount being stored in the liver and is slowly got rid of in the hair and epidermis where it may be found for months even after the drug has disappeared from the urine and faeces.

Acute toxic action.—Colicky pains, severe vomiting and purging, cramps of the legs, intense thirst, prostration and collapse are the prominent symptoms, which may be mistaken for those of

cholera. At the *post-mortem* the stomach and intestine are foun inflamed, with occasional patches of softening of the mucous mem brane. *Fatty degeneration of the liver, kidneys, and heart* is foun if the patient survives long enough. In fulminant cases there ma be no symptom of gastro-enteritis, death takes place from collaps due to withdrawal of blood to the splanchnic area before enteriti develops.

Treatment.—Emetics, apomorphine. The pump must be use with great caution. Moist peroxide of iron freshly prepared b mixing solution of ferric chloride with sodium or ammonium carbo nate and straining rapidly through muslin, or dialysed iron in 1 oz doses diluted, or better still ferri hydroxidum c. magnesii oxide Demulcents, and castor oil to clear the intestine, stimulants, hot water bottles, etc. Dimercaprol (BAL) has replaced all othe systemic treatments.

Chronic toxic action.—Chronic poisoning occurs amongst thos who either handle arsenical pigments, inhale arsenical dust fron wall-paper, dresses, etc., or consume wines* containing traces o arsenic. Loss of appetite, nausea, vomiting, colic, mild diarrhoea oedema of the lower eyelids, conjunctivitis, swelling of the joint are the symptoms generally observed, when arsenic is continue long medicinally in large doses. Peripheral neuritis, muscular para lysis of the limbs, ataxic gait, muscular atrophy, bronzing an patchy pigmentation of the skin and darting pains in the limbs ar also noticed in many cases of slow poisoning. Skin eruptions ar a common accompaniment and are due to the direct action of th drug. Irritation of the mucous membranes of the eye, nose an larynx follows and is analogous to skin eruption.

THERAPEUTICS

Externally.—Arsenic was formerly extensively used as a caustic in the form of paste for destroying new growths, such as lupus, condyloma, epithelioma, warts, etc. Its use has been superseded by surgical measures, radium and deep X-ray.

Internally.—Dental arsenical paste is employed to destroy the tooth-pulp in caries of the tooth, before stopping.

Malaria.—Arsenic is used in the treatment of malaria and its value is more marked in chronic cases accompanied by anaemia and cachexia. Its effect in acute cases is not so marked as quinine, mepacrine or paludrine, but when given with iron and quinine after the acute stage it is certainly of great value. In cases where quinine fails to effect a cure, a combination of quinine and arsenic will be found to yield better results (*see* page 486).

Haemopoietic system.—In Hodgkin's disease (general lymphadenoma) arsenic is a useful remedy. Large lymphomas may be absorbed by its prolonged use. It has been used in **chronic myeloid leukaemia** in large doses but the benefit is only temporary. The usual dose is to start with 5 ms. of the liquor three times a day and gradually increased by one minim every second day till the maximum of 10 ms. is reached. This dose may be further

* Peripheral neuritis was a marked symptom in an outbreak of arsenical poisoning in England, due to drinking contaminated beer.

increased if necessary, but should be stopped as soon as the white cell count comes down to normal.

Arsenic is used in **pernicious anaemia** where it improves the number of red blood corpuscles and the haemoglobin. It is also useful in **microcytic anaemia** and in anaemia following malaria, specially when combined with iron.

Skin.—Chronic skin diseases, especially scaly and papular varieties, improve with arsenic. Psoriasis, lichen, chronic eczema, acne, pemphigus, etc., yield to it. It seems to act specially well in diseases affecting the epidermis rather than other portions of the skin.

Other Uses.—Arsenic has been used in the treatment of asthma, but its use has been replaced by atoxyl or soamin. Its use in chorea is not based on any rational ground.

Prescribing hints.—Solid arsenic is given in pill. For prolonged use Fowler's solution is the best preparation, and the dose should be slowly increased to its therapeutical limit of tolerance. It is contra-indicated when gastric or intestinal irritation is present, such as nausea, loss of appetite, etc. It should always be used after food.

Organic Arsenic Preparations

These compounds have come to occupy an important position among the therapeutical agents for the treatment of several spirochaetal and protozoal diseases, notably syphilis and trypanosomiasis. They belong to two groups, *viz.*, *trivalent* and *pentavalent* compounds, in both of which the arsenic exists in non-ionisable form and therefore they can be given in large doses. They are less toxic than the inorganic salts, and do not possess the specific paralysing effect on the capillaries. They however do not produce their typical action immediately, but are slowly reduced in the body into ionic form by oxidation and other processes, when they become active. They are especially toxic to the invading parasite, though very little parasiticidal effect is seen *in vitro*, possibly they require the co-operation of the host to become parasitotropic. The trivalent compounds are as a rule more effective than the pentavalent compounds. The latter compounds though effective in trypanosomiasis are less valuable in syphilis, possibly due to their rapid excretion which prevents sufficient concentration in the blood for a long time to be effective in syphilis which is a chronic infection.

1. Trivalent Compounds

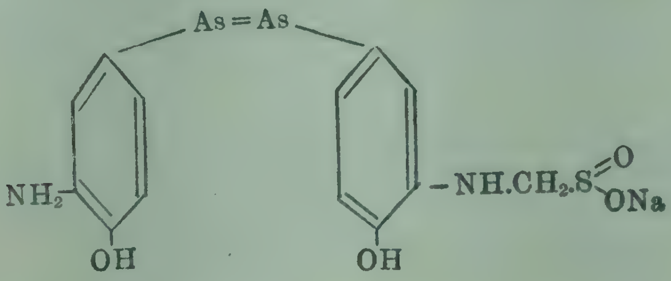
NEOARSPHENAMINA

(Neoarsphenamin.). Neoarsphenamine

Syn.—Novarsenobenzol ; Neosalvarsan ; Novarsenobenzene ; 914.

Source.—May be prepared by treating 3 : 3′-diamino-4 : 4′-dihydroxyarsenobenzene with sodium formaldehydesulphoxylate. It is

distributed in hermetically sealed glass containers, from which air has been evacuated, or replaced by an inert gas. Contains about 20 p. c. arsenic.

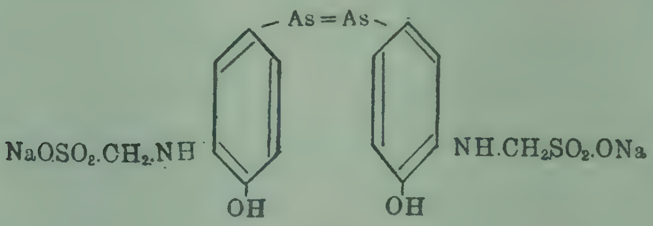


Characters.—A yellow, dry powder, freely mobile in contact with glass surface; odour, none, except that due to traces of ether or alcohol. *Soluble* in water, insoluble in dehydrated alcohol and in solvent ether. A 1 p. c. w/v aqueous solution is neutral, or slightly alkaline, to litmus.

Storage.—It should be kept at a temperature below 15°C. It should not be used if it becomes darker in colour.

B. P. Dose.—2½ to 10 grs. or 0.15 to 0.6 grm. (intravenous injection).

SULPHARSPHENAMINA. (Sulpharsphenamin.). **Syn.**—Sulpharsenobenzene; "Sulfarsenol."—Sulphrasphenamine is prepared by treating 3 : 3′-diamino-4 : 4′-dihydroxyarsenobenzene dihydrochloride with formaldehyde and sodium hydrogen sulphite. Supplied in hermetically sealed glass containers like neoarsphenamine. Contains about 20 p.c. arsenic.



Characters.—A yellow, dry powder, freely mobile in contact with glass surface; no odour, except of alcohol or ether. *Soluble* in water, insoluble in alcohol (95 p. c.), and in solvent ether.

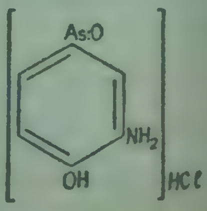
Storage.—It should be kept at a temperature below 15°C. It should not be used if it becomes darker in colour.

B. P. Dose.—1½ to 10 grs. or 0.1 to 0.6 grm. (subcutaneous or intramuscular injection).

Official Preparations

1. **Injectio Neoarsphenaminae.—B. P. Dose.**—*By intravenous injection.*—**2½ to 10 grs. or 0.15 to 0.6 grm.**
2. **Injectio Sulpharsphenaminae.—B. P. Dose.**—*By subcutaneous or intramuscular injection* :—**1½ to 10 grs. or 0.1 to 0.6 grm.**

OXOPHENARSINAE HYDROCHLORIDUM. (Oxophenarsin. Hydrochlor.). Syn.—Mapharsen; Mapharside.—Oxophenarsine Hydrochloride is the hydrochloride of 3-amino-4-hydroxyphenylarsine oxide. Contains 29.5 to 32.0 p.c. of trivalent arsenic and 30.0 to 32.0 p.c. of total arsenic.



Characters.—A white or nearly white powder; odourless. *Soluble* in water, in solutions of alkali hydroxides and carbonates and in dilute mineral acids.

Storage.—Should be kept in hermetically-sealed container at a temperature below 20°.

B. P. Dose.—1/3 to 1 gr. or 20 to 60 mg. *by intravenous injection.*

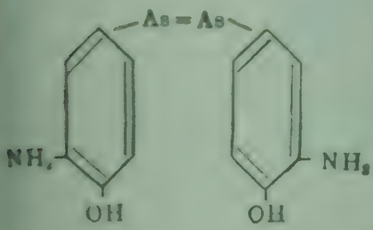
Oxophenarsinae Tartras. (Oxophenarsin. Tart.).—Oxophenarsine Tartrate is the hydrogen tartrate of 3-amino-4 hydroxyphenylarsine oxide. Contains 19.0 to 19.6 p.c. trivalent arsenic and not more than 19.6 p.c. of total arsenic.

Characters.—A white or nearly white powder ; odourless. *Soluble* in 25 parts of water, in alcohol (95 p.c.).

Storage.—Should be kept in hermetically sealed containers at a temp. below 20°.

B. P. Dose.—3/4 to 1½ gr. or 45 to 90 mg. *By intravenous injection.*

Arsphenamina.—Dioxy-diamino-arseno-benzene Dihydrochloride. **Syn.**—Arsenobenzol ; Salvarsan ; 606.



Characters.—A light yellow powder. odourless or has a slight odour. Hygroscopic. In the dry state or in solution it is oxidised by exposure to the air, becoming darker and more toxic. Soluble in water, alcohol, and glycerin. Contains not less than 30 p. c. of arsenic.

N. B.—Preserve in sealed colourless glass tubes from which air has been excluded either by production of a vacuum or by displacement with a non-oxidisable gas.

Dose.—Intravenous, 0.3 grm. (approximately 5 grs.).

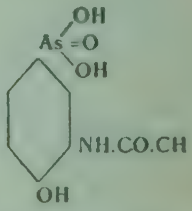
Non-official Preparation

1. **Arsphenamina Argentica.** *Syn.—Silver Salvarsan ; Silver Arshpenamine.*—Contains 15 to 21 p.c. of arsenic and 12 to 13 p.c. of silver. 0.1 grm. corresponds to about 0.2 grm. of arsphenamine or 0.3 grm. of neoarsphenamine. Valuable in syphilis of the central nervous system. **Dose.—1½ to 10 grs. or 0.1 to 0.6 grm.** in 1 p.c. solution intravenously, at an interval of not less than 4 days for men.

2. Pentavalent Compounds

ACETARSOL

Acetarsol



Syn.—Acetarsone ; "Stovarsol".

Source.—It is 3-acetylamino-4-hydroxyphenyl-arsonic acid. Contains 27.0 to 27.4 p. c. As.

Characters.—A white crystalline powder. Almost *insoluble* in cold water, moderately soluble in boiling water, insoluble in alcohol (95 p. c.), and dilute acids ; soluble in dilute alkalies.

B. P. Dose.—1 to 4 grs. or 60 to 250 mg.

TRYPARSAMIDUM. (Tryparsamid.).—Tryparsamide is sodium *N*-phenylglycineamide-*p*-arsonate. Contains 25.1 to 25.5 p.c. of As. in organic combination.

Characters.—A colourless, crystalline powder ; odourless. Freely *soluble* in water ; insoluble, or only slightly soluble in alcohol (95 p.c.), in solvent ether, chloroform, and in benzene.

Storage.—It should be kept in a small well-closed container, protected from light, and stored in a cool place.

B. P. Dose.—15 to 30 grs. or 1 to 2 grms. *by subcutaneous, intramuscular or intravenous injection.*

Official Preparation

1. **Injectio Tryparsamidi.—B. P. Dose.**—*By subcutaneous, intramuscular or intravenous injection* :—**15 to 30 grs. or 1 to 2 grm.**

Non-official Preparations

1. **Sodii Cacodylas, B.P.C.**—*Sodium Dimethylarsonate.* In white, colourless, deliquescent pieces, or as granular, powder. It is used in all cases in which arsenic has been used, and is valuable in chronic skin affections. Given in doses of 1

to 2 grs. *intramuscularly*. Therefore it can be used with less danger of upsetting the stomach. It may also be given in pill form. *Dose.—Hypodermically*, 1/4 to 1 gr. (16 to 60 mg.) but it may be increased to 3 grs. as *maximum single dose*, and as *maximum dose* in 24 hours. If given by mouth or per rectum it may cause renal congestion with a fall of urinary secretion.

2. Di-sodium Methylarsonas. *Syn.—Arrhenal*: "*NewCacodyle*."—Soluble 1 in 1 of water and sparingly in alcohol. Its arsenic content is 25.65 p. c. Its uses are the same as sodium cacodylate. *Dose*.—1/2 to 2 grs. or 30 to 120 mg. by mouth, or hypodermically; the *maximum dose* (single or in 24 hours) being 3 grs. (200 mg.).

3. Sodii Aminarsonas. *Syn.—Soamin*; *Atoxyl*; *Arsamin*.—A white crystalline powder with a saline taste, soluble 1 in 5 of water at body temperature. Solutions, which should be freshly prepared, may be sterilised by boiling five minutes without becoming decomposed. Its arsenic content should be 24 to 25.6 p.c.

Dose.—Per mouth.—3/4 to 3 grs. or 50 to 200 mg. twice daily after food. *Maximum daily dose.*—3 grs. *Hypodermically*, 1 to 3 grs. or 60 to 200 mg. *intramuscularly* high up into upper third of buttock on alternate days. The salt should be dissolved in sterile water. *The maximum of 3 grs. cannot be exceeded with safety.*

USE.—These preparations were used in **trypanosomiasis**, but have been given up in favour of tryparsamide and suramin.

Soamin and the cacodylates have been used in various types of anaemia, locomotor ataxy, relapsing fever, filariasis and chronic skin disease (psoriasis and lichen).

Hypodermically soamin has been found to be of great value in bronchial asthma with eosinophilia* in 1 gr. doses, increased to 3 grs. given twice a week. Administration of alkalies helps its action.

Precautions.—Several cases are on record of blindness due to optic atrophy following its use. This possibly was due to an unsafe dosage being used, but as idiosyncrasy and previous optic degeneration are important factors, it is necessary to proceed with caution when using the remedy. The following are points to which attention should be paid :—

1. Always examine the retina and the disc for degenerative changes before commencing a course of treatment, and if normal, periodically test the vision and look for any contraction of the fields—if any contraction is noticed stop use of the remedy.
2. In cases of renal and hepatic disease, and in arteriosclerosis, do not use the drug, and only use it with great caution for this reason in old patients.
3. When 100 grs. have been given stop for four weeks.

The earliest toxic symptoms to be carefully watched for are insomnia, gastric pain and haziness of vision.

4. **Sodii Acetylarsanilas.** *Syn.—Arsacetin*; *Sodium Acetyl-aminophenylarsonate*.—It has been used in *syphilis* and *trypanosomiasis*. As with atoxyl caution in its use is to be recommended, as cases of blindness have been reported after its use.

Dose.—1/2 gr. or 30 mg. *per os*, three to four times daily. *Intramuscularly* a maximum of 3 grs. in 10 p.c. solution should not be exceeded.

PHARMACOLOGY OF ARSENOBENZOL DERIVATIVES

The introduction of salvasan as a remedy for syphilis is the direct result of the chemotherapeutic studies of Ehrlich, who suggested a parasiticidal action of the drug. The arsenic in arsenobenzol exists in trivalent form; and Voegtlin has suggested that it is inactive in this form but becomes active when it is partly oxidised in the tissues to form arsenoxide. It circulates in the blood in the colloidal form and is very soon deposited in different organs in relatively non-toxic form and that it is doled out in more active form, which acts more powerfully on the *spirochaetes*.

* B. N. Ghosh, *Glasgow Medical Journal*, 1919.

The mode of action of these compounds is an indirect one, and the presence of arsenic within the reticulo-endothelial cells has actually been demonstrated,* while splenectomy experiments in spirochaetal infections have established that infections held in check in animals break into acute manifestations in splenectomised animals and that treatment of these with specific drugs is less effective than in non-splenectomised animals. In fact there is evidence to show that the mortality rate is increased and the cure rate is decreased after splenectomy, and that an intact reticulo-endothelial system is necessary for the full functioning of the chemotherapeutic compounds of arsenic. After an injection no effect is observed on the spirochaetes for 5 to 8 hours and that during this period the arsenic is converted by tissue reaction into a substance lethal to spirochaetes and this effect lasts for 2 to 3 days when the concentration of arsenic in this active form diminishes.

The modern conception of the mechanism of the action of arsphenamines is that they are converted into amino-oxyphenyl arsenoxide (briefly called arsenoxide or mapharsen) in which form they react with the parasite by combining with a sulphydril group and thus interfere with the metabolic process of the organism. Sulphydril group according to this theory represents the chemo-receptor for arsenic.

Absorption and clearance.—After an intravenous injection more than half the arsenic disappears almost immediately from the blood stream and is absorbed by the reticulo-endothelial tissue and therefore stored in the spleen, liver, lung and the kidneys. It is also excreted with sweat, saliva and milk of the lactating women. Very little is absorbed by the rectum.

It is broken down in the body and excreted in the urine and faeces as ionised arsenic. The percentage of arsenic excreted when given intravenously is greater in the faeces than in the urine, although it appears in the urine within a few hours, and not till the third or fourth day that it is found in the stool. The greater part found in the stool is due to rapid elimination through the bile which has a high arsenic content. Excretion is said to be hastened by the administration of potassium iodide. The pentavalent compounds are excreted more rapidly, about 85 p.c. being eliminated within 24 hours. The rate of excretion shows wide individual variation which accounts for the difference in toxicity and therapeutic activity. Damage to the kidneys causes considerable variation in the rate of excretion. Failure to demonstrate the presence of arsenic in the urine should be looked upon with caution as heralding signs of intolerance, jaundice or dermatitis.

* *Jiminez de Asua and Kuhn, 1928.*

After an intravenous injection the drug must circu- late through the brain and the cord, but whether it pene- trates the cerebro-spinal fluid has received much attention While some observers found no trace of arsenic in the brain after intravenous injections of arsphenamine, others (Fordyce, Rosen and Myers) detected in more than 80 p.c of cases, at least during the period of treatment.

Toxic symptoms and other side effects :—

As a rule few cases show any symptoms of poisoning when arsphenamine is injected. According to individual variation, cases have been observed where symptoms of poisoning appeared, and these effects varied from simple disturbance to grave and even fata issues. Some of these cases were due to faulty technique, others from some form of arsenical poisoning, while a few were due to alteration in the colloidal equilibrium of the blood following an injec- tion of a large bulk of fluid. The symptoms may be grouped as follows :—

1. *Immediate reactions.*—In about one-twentieth to five per cent. of cases severe toxic symptoms appear within a few minutes Although alarming they are rarely fatal. The symptoms are those of shock. The face becomes flushed, the conjunctiva injected, tongue and eyelids become oedematous. Nausea, vomiting, profuse perspi- ration, cough, dyspnoea and precordial pain are often present. If stomatitis is present there may be pain in the gums and teeth, or in more severe forms the tongue and lips may become swollen. These symptoms are known as *nitritoid reaction.* They are common with patients with tubercular lesions (Stokes), or when a large volume of fluid is injected, as with salvarsan. They are probably due to some alteration in some blood proteins (flocculation and agglutina- tion), or to the presence in the blood of the breakdown products of spirochaetes, or to liberation of a histamine like substance.

2. *Early toxic symptoms.*—These generally appear within a few hours after administration and are characterised by febrile reaction with chill, nausea and vomiting. There may be severe pains in the body. Kidneys show evidences of damage with albumin and casts As a rule these may be temporary and the symptoms disappear with the stoppage of treatment. Urticarial and other forms of skin erup- tions may appear (*exfoliative dermatitis*). These generally appear after about a week and may be very severe. Skin rash is more common in persons with pre-existing skin disease and when some septic focus is present.

Occasionally the syphilitic process may show an increase in an acute form after the injection. There may be an exacerbation of a syphilitic keratitis resulting in blindness, or deafness, or develop- ment of other types of acute lesion of the central nervous system If the secondary skin lesions are present they become erythematous swell up and show an increase of secretion from the ulcers. This phenomenon, which is known as *Herxheimer reaction*, comes on suddenly and is due to the poisonous action of the proteins (endo- toxins) set free from the spirochaetes. The appearance of any of these symptoms implies that the treatment should be stopped.

3. *Severe late reactions.*—Occasionally severe and even fata symptoms appear a few days after administration. In addition to some of the symptoms already described, the cerebrum and the live may be involved.

The cerebral symptoms (*arsphenamine encephalitis*) appear afte large doses, or when the ordinary doses have been given too quickly The onset is sudden, the symptoms being headache, vomiting, dysp- noea, epileptiform convulsions with clonic spasms, followed by un- consciousness, suppression of urine, dilated pupils, coma and death

generally forty-eight hours after the onset of the symptoms. Haemorrhagic encephalitis occurs during the secondary stage, as a rule after the second injection.

Jaundice appears in the course of treatment and may start suddenly, may be intense and may end fatally. It may be due to syphilitic hepatitis, action of arsphenamine on the liver, allergy, or to intercurrent infection. Three types of jaundice are usually found; they are:

(a) *Early jaundice*, usually commences within a few hours, may appear suddenly, or after subsequent injections.

(b) *Late jaundice* is a more serious disorder and appears several weeks to several months after termination of a course of injections. Unless followed by acute yellow atrophy of the liver, recovery takes place. Liver may be enlarged, with bile and traces of albumin in the urine.

(c) *Acute yellow atrophy of the liver* is a more serious complication and appears some weeks after the end of a course of treatment.

Some rare toxic symptoms have been recorded. They are *purpura haemorrhagica*, *aplastic anaemia* and *agranulocytosis*.

The following factors influence toxicity :—(1) Abnormal toxicity of the drug; (2) errors in technique; and (3) susceptibility of the patient; and are avoided by (1) using a reliable preparation; (2) following the same technique in the preparation and administration of the drug; (3) a preliminary examination of the patient for possible visceral disease; and (4) watching the patient during the whole course of treatment.

Treatment of poisoning.—Since the symptoms of nitritoid reaction resemble anaphylaxis and nitrite poisoning, adrenaline and atropine are suitable remedies. An injection of 1/100 gr. of atropine sulph. half an hour before reduces the risk of severe reaction. Different patients differ in their susceptibility, and in sensitive persons, administration of ephedrine the night before and atropine half an hour before injection may be used as a preventive. By giving one-tenth of the dose an hour before the remainder is given, the toxic symptoms may be averted. The patient should be carefully watched for any of the late toxic symptoms during a course of treatment and if any appear further treatment should be suspended. Nephritis and other symptoms are treated on general lines. Sodium thiosulphate is useful in arsenical dermatitis (*see* page 90). Ascorbic acid is also effective. At first it is given by injection and then by the mouth. Two tablets of 5 mg. or 500 units each by injection three times daily. Nicotinic acid may be tried both as a preventive and also for treatment.

For hepatitis, calcium gluconate, insulin and intravenous glucose. Sodium dehydrocholate 10 mils of 5 p.c. solution mixed with arsphenamine and injected slowly.

For *encephalitis* Schamberg and Wright recommend the following :—Bed; spinal puncture, withdrawing 50 c.c. liquid; venesection, withdrawing 60 to 100 c.c. blood; thorough purging; large doses of bicarbonate of soda; injection of adrenaline, 5 ms. every four hours by day; oxygen inhalation for anoxaemia of the brain.

Recently the use of Dimercaprol (BAL) has superseded all other methods of treatment. (*See* page 532).

THERAPEUTICS

These preparations are largely used in certain types of protozoal and spirochaetal infections, and are of special value in syphilis, Vincent's angina, yaws, etc., and good results have been reported in relapsing fever and rat-bite fever. A single injection of arsenobenzol or any of the

derivatives will cause the spirochaetes to disappear in few hours from the chancre, and since a single dose w not reach all the parasites, the injections are repeat After three injections the Wassermann reaction if p itive becomes negative in most cases, but the improveme is not permanent, for after some weeks or months the r action reappears and the symptoms of secondary syphi begin to appear. The advantage of using arsenoben derivatives is the rapidity of their action, whereas t concentration required to sterilise the system with mercu is obtained after several days or weeks. Therefo after the immediate action has been obtained by the u of arsenic the treatment should be supplemented by t slow and prolonged action of mercury or bismuth. If prop treatment is adopted early during the primary lesion it w prevent secondary symptoms and effect a definite cure.

In the *secondary stage* with definite serum reactio it will cause disappearance of the mucous lesions of t mouth and throat, and the healing of the skin rashes wit in a short time. In the *tertiary stage* the treatme should be combined with courses of iodide. During pre nancy the injections of both neoarsphenamine and bismu should be given, but in small doses, at the same time t kidneys should be watched to avoid developing nephritis

The modern conception of the treatment of syphil with arsenobenzol compounds is not to use a large dose produce a high concentration of the drug in the blood f a limited period, but to maintain a moderate concentr tion for a prolonged period, by giving a series of injectio in moderate doses instead of a single large dose. It h therefore been found necessary to give intramuscular i jections more frequently so as to maintain a moderate co centration of arsenic for a prolonged period to effect com plete recovery.

Some cases of syphilis do not improve under arsen benzol and Ehrlich suggested that the failure was due the parasites inhabiting in out of the way parts of t body, *e.g.* cerebro-spinal fluid, which the drug cann reach. After an injection most of the parasites in t blood stream are killed, but a few surviving ones slow multiply and reinfect the whole system. Since the pr paration of the solution of arsphenamine is complicate and therefore not suited for routine use, and its use w followed by a large number of accidents from errors technique, neoarsphenamine and oxophenarsine have pra tically replaced it.

Silver salvarsan is useful in neurosyphilis, extensi gummatous ulcerations and anaemia.

Oxophenarsine is as effective as neoarsphenamine the treatment of syphilis and undergoes no chemical chang

in the body to be effective. It is less toxic and gives rise to less severe reaction, and is specially valuable in early cases. It is quickly excreted, about 85 to 96 p.c. of arsenic being excreted in 11 days. Since it does not flocculate the blood plasma, nitritoid crises and other immediate reactions are very rare, moreover reactions involving skin and liver are uncommon. The injections should be given twice a week in the first two weeks.

Sulpharsphenamine does not oxidise so easily and is less irritant to the tissues and is convenient for intramuscular injection producing little or no local reaction. It is therefore largely used for children to whom intravenous route is not convenient.

Cerebro-spinal syphilis should be treated with neoarsphenamine and bismuth, or arsphenamine serum may be administered fortnightly by intraspinal or intracisternal injections. Many syphilologists are doubtful regarding the value of this treatment in cerebro-spinal syphilis.

Since tryparsamide has the power of penetrating the central nervous system more readily than other arsenical preparations, it has been used in neurosyphilis, but it has little power in killing spirochaetes and is not of any value in either primary or secondary stages, or against gumma. It has not proved successful in the treatment of early manifestations of cerebro-spinal syphilis, but gives good results in disseminated sclerosis provided it is used before irreparable damage of the nerve cells have resulted and may be combined with malaria treatment. It is said to possess remarkable power of reinforcing processes of natural resistance and promoting recuperation. It is valuable in human trypanosomiasis and has been used in filarial infection and chyluria. For its action in trypanosomiasis, *see* page 544.

Contra-indication.—(1) The injection should never be given on a full stomach, or when the blood pressure is high. (2) It should not be given to persons suffering from hepatic disorders, chronic renal disease (of non-syphilitic origin), diabetes, or chronic myocardial degeneration, or to cases exhibiting evidences of recent endocarditis. (3) Owing to the congestive action of this drug it should not be used in cases with signs of active pulmonary tuberculosis, fetid bronchiectasis, or serious lung disease. (4) Patients whose vessels are atheromatous or who have suffered from cerebral haemorrhage are also bad subjects for salvarsan. (5) Persons showing special idiosyncrasy to arsenic. (6) Persons suffering from non-syphilitic retinal diseases or affections of the optic nerve. (7) Advanced cerebral mischief and cachexia. (8) Patients suffering from certain skin disease, specially eczematous or seborrhoeic type. (9) Those suffering from advanced diabetes or Addison's disease.

Prescribing hints.—These compounds are powerful irritants to the stomach and are broken down in the gastro-intestinal tract; they are therefore used by the intravenous route, except sulpharsphenamine which may be administered subcutaneously or intramuscularly. Solution of arsphenamine or neoarsphenamine given subcutaneously produce local irritation and inflammation. These

effects are due partly to the drug and partly to the reaction of th solution, acid solutions cause severe and persistent pain, while alka line solutions produce corrosion, ulceration and even gangren Neoarsphenamine though forms a neutral solution also produce severe pain, inflammation and fibrosis. The usual method is th intravenous route. It is practically painless and there is seldo objectionable local effects at the point of injection ; if any shoul arise it may be ascribed to faulty technique. Moreover the tim spent in bed is greatly reduced by this method. Whatever metho is used strictest asepsis must be maintained. These injections shoul be followed by administration of bismuth. Rectal administratio has also been suggested but is not so effective. When intensiv treatment is required, a series of six intravenous injections, once week constitutes a course. The dose should always be varied wit the strength and condition of the patient. It has been found tha smaller doses frequently repeated give as good results as full dose and are less dangerous to the patient.

Provocative injection.—In cases where serological tests giv negative results and to secure definite results, provocative injectio of neoarsphenamine may be given. This may be done in one of th following ways :—

(a) A single injection of 0.3 or 0.45 grm. followed by seve daily Wassermann reaction with daily observation of the patient.

(b) Two injections at an interval of five days and Wasserman reaction carried out 13 to 15 days after the 2nd injection.

Spinal Injection of Arsphenamine Serum.—Since very littl arsenic passes into the central nervous system, intravenous use o arsphenamine is not very useful in cerebro-spinal syphilis. It ha therefore been suggested that in these cases salvarsanised serur may be injected directly into the spinal canal. The results hav been rather hopeful specially in the treatment of tabes.

Swift-Ellis Method.—The patient is given an ordinary dose o arsphenamine or neoarsphenamine intravenously, and after an hou 40 mil of blood is withdrawn from a vein, which is allowed to clo and left for 24 hours on ice ; 12 to 15 mil. of serum is then draw off and centrifugalised. This serum contains about 0.01 mg. o arsphenamine per mil. It is heated to 56°C. for half an hour. Thi may be diluted with normal saline to make 30 mil. and injected b lumbar puncture, an equal volume of cerebro-spinal fluid being firs withdrawn. The injections are safe and may be repeated after tw weeks.

Acetylarsan (diethylamine hydroxyacetylaminopheny arsonate) a pentavalent compound used successfully i **tropical eosiniphilia** with symptoms of **asthma** in preferenc to soamin, being less toxic. Used by subcutaneous o intramuscular injection every 4 to 6 days in doses of 1 t 3 mils containing 0.05 grm. of arsenic per mil.

DIMERCAPROL. (Dimercap.). Syn.—British Anti-Lewisite B.A.L.—Dimercaprol is 2 : 3-dimercaptopropanol. Contains betwee 98.5 to 101.5 p.c. of $CH_2(SH).CH(SH).CH_2OH$.

Characters.—A colourless or slightly yellow clear liquid ; odour, alliaceous *Soluble* at 15° in 16.7 parts of water.

NON-OFFICIAL PREPARATION

1. **Injectio Dimercaprolis. B.P.C.** *Syn.—Injection of B.A.L.*—Dimercapro 5 grm., benzyl benzoate 9.6 mil, arachis oil, q.s. 100 mil. *Dose.*—To be determine by the physician.

Action and Uses

Dimercaprol was originally used as an effective antidote for neutralising the effects of lewisite an arsenic gas used during the World War II.

On the idea that the toxic effects of arsenic are supposed to be due to its affinity for the sulphydryl (-SH) compounds essential for biologic oxidation and reduction processes of living cells, it was argued that detoxification of arsenic may be accomplished by administration of substances containing thiol group. It has been shown that "dithiol' derivatives (two-SH groups) have greater affinity for certain arsenicals and form more stable non-toxic compounds than the thiol proteins in the tissues. Dimercaprol is a dithiol compound and offers competition for arsenic and thus protects the tissue proteins. It not only prevents the toxic action of arsenicals but reverses it provided the toxicity has not been prolonged too long. Its use has therefore been advocated in haemorrhagic encephalitis, fever, dermatitis and other toxic manifestations of arsenical therapy. It has also been used in mercurial, gold, bismuth and antimony poisoning. Larger doses are necessary for acute mercurial poisoning.

Dose.—*Severe cases* :—3 mg./kg. every four hours, six times a day for 2 days ; 4 injections on the third day, thereafter 2 injections for ten days or till recovery.

Mild cases :—2.5 mg./kg. of body weight 4 times a day for 2 days ; twice on the 3rd day ; once or twice daily thereafter for 10 days or till recovery.

Administration.—BAL is generally administered intramuscularly in 5 or 10 p.c. solution in pea nut oil containing 10 or 20 p.c. benzyl benzoate to make it more soluble.

Toxicity.—BAL is not free from toxicity and symptoms may appear 15 to 20 minutes after intramuscular injection. Since however the drug is rapidly excreted by the kidneys the symptoms are short-lived. It may cause nausea, malaise, vomiting, salivation, headache, conjunctival oedema, burning sensation of the lips, mouth, throat and eye, burning and tingling of the extremities, constriction of the throat and chest, acceleration of the pulse and rise of blood pressure (both systolic and diastolic). Locally applied it causes urticarial eruption, and sensitisation of the skin. Barbiturates have been recommended for severe side effects of BAL.

POTASSII IODIDUM

(Pot. Iod.)

Source.—Potassium Iodide is obtained by the action of excess of iodine on a solution of potassium hydroxide. Contains not less than 99 p.c. of potassium iodide.

Characters.—Colourless, transparent or somewhat opaque, crystals, or a white granular powder. Odourless ; taste, saline, slightly bitter. *Soluble* in 0.7 part of water, in 12 parts of alcohol (90 p. c.), in 2 parts of glycerin.

Incompatibles.—Bismuth subnitrate, spiritus aetheris nitrosi, solutions of ferric salts, dilute hydrochloric acid, liq. strych. hydrochlor., potassium chlorate, alkaloidal salts, and substances containing starch.

B. P. Dose.—5 to 30 grs. or 0.3 to 2 grms.
Enters into.—Liq. Iodi Aquosus, Liq. Iodi Fort. and Mit.

SODII IODIDUM. (Sod. Iod.).—Sodium Iodide is prepared from iodine and a solution of sodium hydroxide. Contains not less than 99 p.c. of pure sodium iodide.

Characters.—A white, crystalline powder ; deliquescent, having a saline and somewhat bitter taste. *Solubility.* Less than 1 part of water, 1 in 3 of alcohol (90 p. c.).

B. P. Dose.—5 to 30 grs. or 0.3 to 2 grms.

Non-official Preparation

1. **Ammonii Iodidum.**—In minute colourless cubical crystals, or as wh granular powder. Very hygroscopic. *Dose.*—2 to 6 grs. or 0.12 to 0.4 gm.

Pharmacology of Iodides

Internally.—The action of iodides is identical wit that of iodine, except that these are less irritant to th gastro-intestinal tract, and are therefore used in prefer ence to iodine. Large doses cause irritation of the stomac and give rise to nausea and vomiting if used in concentrate solution. On the other hand the acid may liberate highl irritating iodine.

Iodides are absorbed by the intestine and circulate i ionic form or as compounds with lipoids. They penetrat the different tissues of the body, but apparently concen trate largely in pathological tissues. Iodide is excrete with the saliva within a short time and gives a metalli taste in the mouth. In large doses it produces a group o symptoms known as **iodism.** Besides the characteristi action of iodine, iodides increase the secretion of bronchia glands during elimination through the respiratory mucou membrane, producing a flow of thin mucus, and liquefyin tenacious secretion. Iodides tend to lessen viscosity of th blood, dilate peripheral arterioles and reduce irritabilit of the heart without affecting its contractility.

They are **diuretics** and act possibly by diminishin reabsorption from the tubules like other alkaline salts.

As the spirochaetes of syphilis are not killed by th application of iodide to a syphilitic lesion, it does not ac as a parasiticide. The specific effects in the tertiary stag are exerted not on the parasites but upon the tissues i which the parasites live and which have reacted to thei presence by the formation of gumma. These dissolv under the action of iodides. They combine with anti trypsin which normally prevents the resolution of necroti tissue and set free proteolytic ferments which digest an absorb gummatous tissue.

Iodine is contained in the form of thyroxine in th thyroid gland, and administration of iodine or iodides in creases the iodine content of the gland with correspondin increase of its activity. In persons with abnormal thyroi gland, iodides, or any preparation of iodine often give ris to symptoms which are attributed to over function of th thyroid gland and are quite distinct from iodism, bein symptoms of hyperthyroidism, i.e. cause acceleration of th heart, tremor, nervousness, sleeplessness and increase metabolism.

Elimination.—Iodides are rapidly eliminated mainl by the urine, but partly also by the saliva, gastric juice sweat, milk and other secretions and body fluids and effu-

sions. Seventy-five per cent. of the dose appears in the urine within twenty-four hours. The remainder may remain in organic combination in the body. Swift reported that iodine was not found in the cerebro-spinal fluid even after very large doses given by the mouth. Later Campbell and Snodgrass demonstrated iodine in the same fluid after oral use, and in larger amount after intravenous use.

Untoward effects.—Iodides sometimes give rise to certain symptoms either when continued for a long time in large doses or even with small doses due to idiosyncrasy. They are manifestations of irritative phenomena of the skin and the mucous membranes.

Skin.—In escaping through the skin they produce cutaneous eruptions, vesicular, bullous or haemorrhagic, starting from the papillary layers and not from the sweat glands. All these reactions are due to the iodine set free in the skin glands by oxidation. Serious eruptions usually occur in patients with low vitality, and in those with chronic nephritis. They are less common at the beginning of treatment than the catarrh of the respiratory passages. Cleanliness of the skin and small doses of arsenic are the best prophylactics.

Mucous membranes.—The mucous membranes of the nose, throat, bronchi, conjunctiva, etc., are irritated by iodides giving rise to symptoms of iodism. There is running of the nose, oedema around the eyelids, sneezing and headache, the symptoms resembling acute cold or influenza. Sometimes there may be oedema of the glottis with swelling of the parotid glands, a metallic taste in the mouth, loss of appetite, furred tongue, and salivation ; while vomiting and diarrhoea may appear in more severe cases. Sometimes the symptoms disappear after the dose is increased, and are more common when the excretion is interfered with as in those suffering from nephritis, and disappear with the stoppage of the drug. The cause of these symptoms is not clearly understood. They are not due to liberation of iodine, nor to anaphylaxis, but are supposed to be due to alteration in the colloid equilibrium (Sollmann). It has been shown that intravenous injection of iodides alters the surface relation of the blood, and that these produce oedema from altered colloid-water affinity.

Treatment.—Carbonate of ammonium, sp. ammon. aromat., or bicarbonate of sodium controls iodism. Fowler's solution prevents skin eruptions. Calcium lactate is also used.

Therapeutics of Iodides

Internally.—Iodides are employed in the same class of diseases where iodine is indicated but the following deserve a special notice :—

Respiratory passage.—As the iodides make the phlegm less viscid and help expectoration, they are often used in bronchitis, broncho-pneumonia and pneumonia. But since they produce hyperaemia and excite secretion of the respiratory mucous membrane, they are contra-indicated in acute bronchitis and other acute forms of respiratory troubles, *e.g.* in the early stage of pneumonia. They are helpful when the condition is chronic and the sputum more tenacious, as for instance in asthma and asthmatic bron-

chitis. Although iodides have no action on the bronchial muscles they are used in bronchial asthma in 5 to 10 gr. doses, often with benefit. In pleurisy they help absorption of pleuritic fluid. In pulmonary tuberculosis they increase both the cough and expectoration and in some cases may accelerate haemoptysis. By breaking the tubercular nodules they may cause fresh infection by freeing the bacilli.

Heart and circulation.—Iodides are used to absorb the effusion in pericarditis, and the deposits over the valves. They are extremely valuable in all conditions of the heart and the vessels which follow tertiary manifestations of syphilis. They often give relief to pain of aneurism. Prolonged use sometimes **lowers the blood pressure,** but as a rule fails unless of syphilitic origin. It is believed that it helps to bring pressure down by its action on the carotid sinus (page 302) provided there is scleresis of the sinus. Beneficial results have been obtained in **angina** by giving iodine and iodides intravenously, and by subcutaneous injections of CO_2 ; both may be used either alternately or simultaneously. It is a valuable remedy in arteriosclerosis and Stockman has suggested that the value of this drug is due to production of a large amount of thyroxine.

Scrofula.—The iodides, especially syrupus ferri iodidi, either alone or with cod-liver oil, have a remarkable effect in tuberculosis when the glands are affected.

Syphilis.—Although iodides have no toxic effects on treponema, sodium iodide has given good results in locomotor ataxy used intravenously (1 to 3 grms. in 10 p.c. solution). They are of immense value in tertiary syphilis, or rather in the manifestations of untreated syphilis which go to the tertiary stage. Periostitis, nodes, gummata, syphilitic deposits in the brain and other organs as also certain tertiary skin disease improve with remarkable rapidity, specially when the treatment is associated with injections of antisyphilitic remedies like organic arsenic compounds or bismuth. Success depends upon boldly pushing the drug in doses of 20 to 40 grs. or even 60 grs. three times a day. Iodides sometimes do good in the secondary stage specially when combined with mercury. They have no effect in the primary stage, but are efficacious in congenital syphilis.

Goitre.—Iodine or iodides in small doses (2 grs. daily) sometimes produce good results in simple hypertrophic goitre and have been used both for prevention and treatment. But the patient requires to be constantly watched to prevent the symptoms of hyperthyroidism which may develop if the dose is large and used for a prolonged period. In Graves' disease its use has proved beneficial in reducing the metabolic rate prior to partial thyroidectomy.

It is of value in **actinomycosis or sporotrichosis** in 60 to 120 grs. doses given daily.

Metallic poisons.—Iodides increase excretion of lead and mercury and other metallic poisons from the system; magnesium sulphate should always be given in these cases in combination with the iodide, otherwise the metallic salt may be reabsorbed from the bowels.

Prescribing hints.—Potassium iodide is best administered freely diluted in water or milk, preferably an hour after food. When taken in this way the chances of iodism are less. While some patients suffer from iodism within a few hours after a relatively small dose, others bear quite large doses. Given soon after meals, it may cause gastric irritation from liberation of iodine, but taken half an hour **before meals it is free from this effect.**

As they are incompatible with too many drugs, iodides should preferably be prescribed alone. They are incompatible with alkaloidal salts, and should not be prescribed with liquor strych. hydrochlor. which will throw down alkaloidal precipitate. Potassium iodide should not be used with calomel as it forms a highly irritating and toxic iodide of mercury. Acids for the most part decompose iodides setting free iodine. The same is true with hydrogen peroxide. Iodides precipitate heavy metals. When prescribed with ferric salts iodine is liberated, also when combined with spiritus aetheris nitrosi, if acid. When combined with subnitrate of bismuth the mixture turns yellow from free iodine and from formation of iodide of bismuth.

CLASS C: Drugs used in Leishmaniasis

1. Trivalent Antimony Compounds

ANTIMONII ET POTASSII TARTRAS

(Antim. et Pot. Tart.)

Syn.—Antimonium Tartaratum; Tartar Emetic.

Source.—Potassium Antimonyltartrate is obtained by the interaction of antimonious oxide and potassium acid tartrate. Contains not less than 99 p.c. potassium antimonyltartrate.

Characters.—Colourless, transparent crystals, or a white, granular powder; efflorescent; taste, sweet, no odour. *Soluble* in 17 parts of water, in 3 parts of boiling water, insoluble in alcohol (90 p.c.).

B. P. Dose.—1/32 to 1/8 gr. or 2 to 8 mg. *Emetic.*—1/2 to 1 gr. or 30 to 60 mg. *Intravenously.*—1/2 to 2 grs. or 30 to 120 mg.

OFFICIAL PREPARATION

1. Injectio Antimonii et Potassii Tartratis.—B. P. Dose.—1/2 to 2 grs. or 30 to 120 mg. N. B. When no strength is stated, 1/3 gr. in 15 ms. shall be dispensed.

Note.—Solution for injection may be sterilised by heating in an autoclave, or by filtration.

ANTIMONII ET SODII TARTRAS. (Antim. et Sod. Tart.).—Sodium Antimonyltartrate may be obtained by the interaction of antimonious oxide and sodium acid tartrate.

Characters.—Colourless and transparent, or whitish, scales or powder. No odour; taste sweetish. Hygroscopic. *Soluble* in 1.5 parts of water, insoluble in alcohol (90 p.c.).

B. P. Dose.—1/32 to 1/8 gr. or 2 to 8 mg. *Emetic.*—1/2 to 1 gr. or 30 to 60 mg. *Intravenously.*—1/2 to 2 grs. or 30 to 120 mg.

OFFICIAL PREPARATION

1. Injectio Antimonii et Sodii Tartratis.—B. P. Dose.—1/2 to 2 grs. or 30 to 120 mg. N. B. When no strength is stated, 1 gr. in 15 ms. shall be dispensed.

Additional Trivalent Compounds

Stibophenum.—See page 543.

Antimony Sodium Thioglycollate, U. S. P.—Less toxic and more effective than tartar emetic. Useful in granuloma venereum (granuloma inguinale due to Leishmania donovani) also in kala-azar in doses of 3/4 to 1½ gr. (50 to 100 mg.) in 10 to 20 mil water for injection every 3rd or 4th day, either intramuscularly or intravenously. **Dose, U. S. P.**—3/4 gr. or 50 mg.

Anthiomaline.—Lithium Antimony Thiomalate. Contains 16 p.c. antimony. Useful in trypanosomiasis, leishmaniasis, filariasis (*W. bancrofti*) and other infections where antimony is indicated. Striking results in lymphogranuloma and bilharziasis. Produces less emesis and can be given in large doses. Supplied in 6 p. c. solution. 1 mil contains 60 mg.

Dose.—For bilharziasis :—2 mil of 6 p.c. solution on alternate days for 10 injections. For lymphogranuloma inguinale :—0.5 to a maximum of 2 mils in 12 to 15 injections. For filaria :—2 to 4 mil up to 10 injections. In all these conditions use smaller doses first and increase gradually.

Antimosan.—Von Heyden 661.—Contains 12.5 p.c. antimony.

Dose.—3 grs. or 0.2 grm. either intramuscularly or intravenously.

2. Pentavalent Compounds

Urea Stibaminum, I. P. L. Syn.—Stiburea.—Urea Stibamine is obtained by the interaction of *p*-aminophenylstibinic acid with urea. Contains 38 to 42 p.c. antimony.

Characters.—A pale greyish, pale brownish or pinkish, amorphous, dry powder free from grittiness and freely mobile in contact with glass surface. Readily *soluble* in cold water, partly soluble in dehydrated alcohol.

Storage.—It should be kept in perfectly dry and sterile ampoules, sealed under partial vacuum and under nitrogen at temperature below 30°C. If becomes darker in colour, or the colour is significantly changed, it should not be used.

Dose.—3/4 to 3 grs. or 0.05 to 0.2 grm. By intravenous injection.

Stibenyl.—Sodium acetyl-*p*-aminophenylstibinate. A brownish powder soluble in 10 parts of water. First pentavalent compound used in kala-azar. Results have not been encouraging. Can be given intramuscularly.

Dose.—3/4 to 1½ grs. or 50 to 100 mg.

Stibosan. Syn.—Von Heyden 471.—It is sodium-*m*-chlor-*p*-acetyl-aminophenylstibinate. Useful in kala-azar and rat-bite fever.

Dose.—3 to 5 grs. or 0.2 to 0.3 grm. Solution should not be boiled and should be prepared fresh to make 1 to 2 p.c. solution. A stable compound and does not undergo any change when exposed to air. Inferior to other antimony salts in granuloma venereum.

Neostibosan. Syn.—Von Heyden 693 B.—It is diethylamine-*p*-aminophenyl-stibinate. Contains 41 to 44 p. c. antimony. Generally given in 5 p.c. solution, although 25 p.c. solution may be used. Can be given intramuscularly, therefore useful for children. Injections may be given daily but preferable on alternate days. Intramuscular injections give as good results as intravenous injection. Solution should be prepared fresh. About 10 injections are required in an average case of kala-azar. Intial dose for an adult is 0.1 grm., the second 0.2 grm., the third 0.3 grm. A total of 3.5 to 5 grm. is usually necessary to effect a cure. Gives satisfactory result in filaria.

Solustibosan.—The metal is present in the form of sodium antimonyl gluconate. Supposed to be superior to neostibosan in kala-azar. Can be administered intramuscularly and intravenously. Issued in sterile soluble isotonic neutral solution in water, so that 1 mil contains 20 mg. of antimony. 2 mil is approximately equal to

0.1 grm. of neostibosan. In infantile kala-azar given in oily suspension intramuscularly 2 mil for each kilo of body weight. 1 mil being equal to 0.054 grm. Ordinarily ten daily injections are given which are well tolerated.

PHARMACOLOGY

Externally.—Salts of antimony are powerful **irritants** to the skin and form characteristic local lesions, first papular, then vesicular and lastly pustular. These rashes resemble small-pox and are due to the formation of insoluble irritant precipitates at the orifices of the sweat glands by the acid perspiration. The pustules sometimes coalesce and form a big ulcer which on healing leaves an **unsightly scar.**

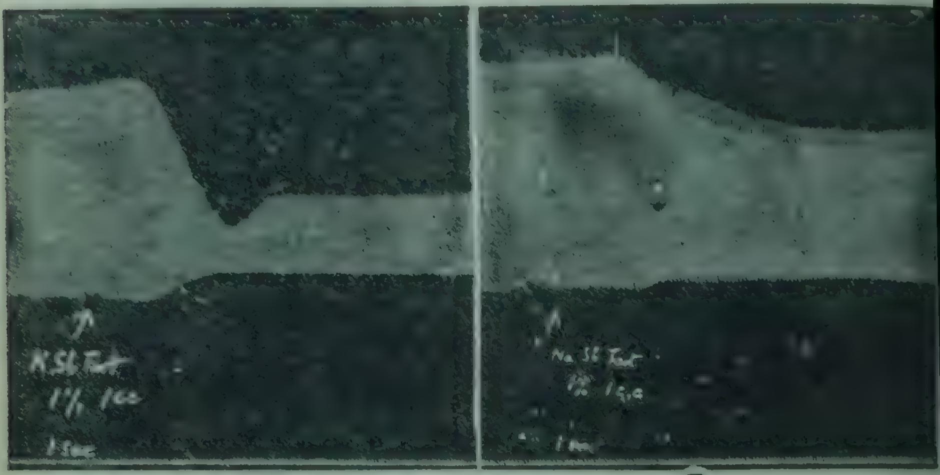
Internally.—In the stomach antimony has the same irritant action as observed on the skin, but the degree of irritation depends upon the amount used. In small doses it produces a sense of warmth and soreness, and in large doses loss of appetite, nausea and increased secretion of gastro-intestinal mucus. In still larger doses (1 to 2 grs.) it induces **vomiting** due to direct irritant action on the stomach which is accompanied by depression, cold perspiration, hurried respiration and increased bronchial and salivary secretion. The salts dissociate in the stomach and intestine and increase their peristaltic movement. But the antimony ion is slowly absorbed from the stomach, therefore the effects are entirely confined to the stomach, and since most of it is expelled out very little enters the intestine, unless a large quantity is used, or more passes into the intestine than is expelled out by the vomit. In toxic doses it is a powerful **gastro-intestinal irritant** like arsenic.

Heart and circulation.—Even in small doses, antimony reduces the force and frequency of the cardiac beat which tends to become intermittent, and in large doses the heart becomes profoundly depressed with acceleration of the pulse-rate. The blood pressure falls considerably (1) partly from the depressed condition of the heart, (2) partly from the relaxed state of the arterioles caused by the depression of some portion of the vaso-motor system, and (3) partly reflexly from the stomach (nausea).

Respiration.—Respiration is very much depressed after a brief acceleration. Inspiration becomes short, expiration prolonged, and finally respiratory movements become irregular. In fatal poisoning the lungs become congested. It increases the bronchial secretion and helps expectoration. This effect is chiefly reflex from gastric irritation.

Temperature is not much affected in health but is reduced in fevers, owing chiefly to diaphoresis, caused by (1)

the depressed condition of the circulation, and (2) dilatation of the peripheral vessels.



A B

Fig. 36.—Perfusion of isolated Heart of Rabbit. A. Showing the effect of potassium antimony tartrate (1 mil of 1 p.c. solution). B. Effect of sodium antimony tartrate (1 mil of 1 p.c. solution). Note weakening and slowing of the heart, the effect is more marked with potassium salt.

Micro-organisms.—Like arsenic, antimony in dilution of 1 in 200,000 kills **trypanosomes**, and the trivalent antimony, whether in organic or inorganic combinations, is more toxic than the pentavalent form. Pentavalent compounds like neostibosan are slowly converted into trivalent compounds, therefore these are less toxic, produce more sustained action and larger doses can be given. Noguchi has pointed out that the highest dilution of tartar emetic lethal to cultures of leishmania is 1 in 100 *in vitro*, and that its action is not increased by contact with fresh animal tissue. In the body its concentration is not likely to be greater at any time than 1 in 10,000. Moreover, pentavalent compounds are excreted more rapidly than trivalent derivatives. In fact Brahmachari has shown that 30 to 40 p.c. of urea stibamine is excreted within 24 hours after injection, whereas only 6 p.c. of tartrate is excreted in the same period. It is evident therefore that antimony by itself cannot cure kala-azar, and it has been suggested that either it forms a new compound with the tissues of the host which exerts a parasiticidal effect, or that it liberates immune bodies which destroy the parasites.

Elimination.—Absorption of antimony is slow, the salts are excreted by the kidneys, bile, skin, mucous membrane of the bronchi, gastro-intestinal tract and mammary glands. A portion is stored up in the liver. A considerable amount is excreted by the intestine, a large portion is also thrown out by the kidneys.

Therapeutics

Externally.—As a *counter-irritant*, tartarated antimony ointment (5 p.c.) is used in cases of **kala-azar** of children who cannot be given intravenous injections. Application of 1 to 2 p.c. tartar emetic ointment has given good results in the treatment of **oriental sores.**

Internally. **Gastro-intestinal tract.**—As an *emetic*, tartar emetic is not suitable in cases of poisoning on account of its tardy action and the general prostration it induces, but is of great service in those cases of acute inflammatory affections of the respiratory tract, such as croup and bronchitis where both emesis and vascular depression are needed. It is only used in cases of bronchial affections of children in combination with ipecacuanha tincture.

Specific use.—Antimony is chiefly used in the treatment of several tropical diseases, such as leishmaniasis, trypanosomiasis, yaws and bilharziasis. It has also been used in malaria and filariasis, but the results have not been encouraging.

The treatment of **leishmaniasis** with antimony preparations constitutes one of the most important advances in chemotherapy. The best results are obtained when the treatment is commenced early. In fact 18 to 25 injections of tartar emetic or sodium antimonyltartrate spread over two to three months will effect complete recovery. The routine method is to give these injections intravenously, commencing with 0.5 mil of a 2 p.c. solution and gradually increasing the dose by the same amount each week till a maximum of 4 to 5 mils is reached or until 2 to 3 grms. have been given. These injections can be given every 2 to 3 days as long as no toxic symptoms or any excessive reaction occur. Some prefer 1 p.c. solution. If any fluid escapes into the tissues around the vein there will be pain and inflammatory induration. According to Napier the maximum curative dose of tartrate is 4 grms. for every 100 pound of body weight. In practice however a maximum of 2.52 grms. in 30 injections is sufficient. The total amount required to produce complete cure possibly varies. For children or debilitated patients the initial dose should be 0.25 mil. Children tolerate relatively larger doses than adults.

The success of the antimony treatment has led to the introduction of many preparations, but urea-stibamine of Brahmachari gives the best results, and cases resistant to tartrates or other preparations recover under its use. Although it is claimed by some workers that neostibosan is superior to many other preparations inasmuch as it effects a cure with eight daily injections, the results have not been so brilliant as anticipated, and it has no advantage

except that it can be given intramuscularly. An adequate course of urea-stibamine in kala-azar for an adult is 1.5 to 2.5 grms., that for neostibosan is 4.0 to 5.0 grms. Urea-stibamine is therefore more potent. In dermal leishmaniasis the treatment is more prolonged.

Owing to the toxicity of the potassium salt, sodium tartrate of antimony is preferred by many in the treatment of **bilharziasis.** The routine method is to start with ½ gr. dissolved in normal saline, and increase by ½ gr. with each injection till a maximum of 2 grs. is reached. These injections are given on every alternate days. For children the initial dose is ¼ gr. Not more than 25 to 30 grs. are given during the whole course. "Rheumatic pains" after the fourth or fifth injection, appearing at night, may occur as also increased haematuria.

Caution.—The intravenous injection is contra-indicated where any pulmonary or gastro-intestinal complications are present. It should not also be given to patients suffering from chronic renal troubles or to those with feeble pulse and low blood pressure.

Toxic symptoms associated with intravenous injections.—As a rule no untoward symptoms are noticed in the majority of cases provided the treatment is commenced with small doses and gradually worked up to the maximum doses. A certain number of patients however show an intolerance to the drug, and untoward symptoms may appear even after a very moderate dose. These symptoms are more common when trivalent compounds are used. They may be classified as follows : (*a*) Gastro-intestinal symptoms ; severe fits of coughing and retching immediately after an injection are very common. Nausea and vomiting and sometimes acute diarrhoea may follow an injection. (*b*) A slight rise of temperature with or without rigor, this is of no significance unless excessive. (*c*) Cyanosis, rapid and irregular pulse. (*d*) Nervous symptoms. General depression when the treatment has been continued long, persistent headache and hemicrania. Rarely loss of consciousness and incontinence of urine and faeces. (*e*) Pain on the shoulders and in the big joints. (*f*) Papular eruptions. (*g*) Symptoms suggestive of acute hepatitis with jaundice and recurrence of fever. (*h*) Anaphylactic-like syndrome. Generally occurs suddenly after the 6th or 7th injection. Face becomes puffy, urticarial rashes appear all over the body, and difficulty of breathing. In severe cases pulse becomes imperceptible and collapse sets in with stertorous breathing and unconsciousness. These symptoms disappear soon. Though alarming no deaths have been reported.

Appearance of any of these symptoms demands either reduction of the dose or stoppage of treatment.

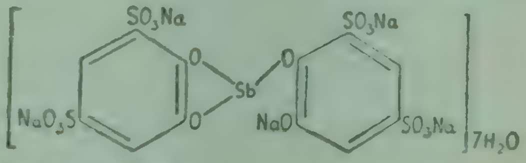
Prescribing hints.—The use of antimony in the treatment of kala-azar is almost universal and the student should know its different methods of administration. In case of children, or where its intravenous use is otherwise contra-indicated, tartar emetic ointment 5 p.c. or metallic antimony 5 to 10 p.c. in lanolin may be rubbed on the skin. Only small doses can be given by the mouth, and therefore in the treatment of protozoal diseases where stronger concentration is required this method is of no use. Intramuscular injections are very irritating and painful, producing severe inflammation. Although several preparations are now available which are claimed to have the advantage of not producing any local effect, the intravenous route is the only reliable method and should always be

slowly. The injection is given with the patient lying down and this position should be maintained for half an hour or longer if necessary. The injection should not be given unless the physician is certain of the needle being in the lumen of the vein. The solution of sodium antimony tartrate can be sterilised by boiling. No food should be given for one hour after injection. Some patients are **intolerant to even small doses of antimony.**

STIBOPHENUM. (Stibophen.). Syn.—Fouadin ; Neoantimosan.

Source.—Stibophen is sodium-antimony-bispyrocatechol-3 : 5-sodium disulphonate. It contains 15.6 to 16.0 p. c. of trivalent antimony, and 16.5 to 16.9 p.c. of sulphur, S, both calculated with reference **to the anhydrous substance.**

Characters.—Colourless, fine, somewhat glistening, crystalline powder ; odourless. Readily soluble in cold water ; almost insoluble in dehydrated alcohol, in solvent ether, in chloroform, in acetone, **and in light petroleum. A neutral solution in water is at first colourless, but soon acquires a yellowish tint, finally reaching a maximum lemon-yellow colour. If the colourless solution is made acid to solution of litmus, the formation of the yellow colour is prevented.**



$C_{12}H_4O_{16}S_4SbNa_5,7H_2O$.

B. P. Dose.—1½ to 5 grs. or 0.1 to 0.3 grm. by intravenous injection.

Official Preparation

1. **Injectio Stibopheni.**—Contains about 5 grs. in 75 ms. **B. P. Dose.—25 to 75 ms. or 1.5 to 5 mil. By intravenous injection.**

Action and Uses

Stibophen is a trivalent compound and is of great value in the treatment of **bilharziasis** due to different varieties of *Schistosoma* and is preferable to sodium antimonyltartrate. It is however not so satisfactory in kala-azar as the pentavalent compounds. It is usually administered intravenously but may be given intramuscularly into the gluteal muscle. The usual dose is 1.5 mils of a 6.3 p. c. w/v solution on the first day, 3.5 mils on the second day and 5 mils on the third day, after which the same dose is given on alternate days till the fifteenth day or a total of 40 to 75 mils have been given ; 5 mils contain 42.5 mg. of antimony. A similar course of treatment has been found effective in **undulant fever** and in **granuloma inguinale** in which disease it gives better result when used in conjunction with oral administration of sulphanilamide. It has been found useful in **filariasis.** It is also a valuable remedy in **trichinosis** and if used early will subdue symptoms and eventually cure in majority of cases.

Stibophen is excreted chiefly with the urine. As a rule it does not produce any toxic symptoms or local reaction, though nausea and vomiting with epigastric pain may occur or there may be some damage to the liver after prolonged use.

Stilbamidine. (*Not official*). Syn.—M & B 744.—It is 4 : 4'-diamidino-stilbene dihydrochloride. In white crystalline powder, soluble in 100 parts of water. **Dose.**—1 to 2 mg. per kg. of body weight intravenously. The solution should be administered slowly.

Action and Uses.—It is a non-antimony compound with chemo therapeutic effect on *L. donovani* infections, and has given satisfactory clinical results in Indian and Sudan variety of kala-azar and i Mediterranean visceral **leismaniasis**. But it produces toxic reactions both immediate and delayed. Immediate reactions are flushing of the face, nausea, headache, rapid pulse, sweating, retching, and occasionally vomiting with fall of blood pressure. The delayed reactions are neuritis and hepatitis. There may be thrombosis of the vein at the site of injection. Cases of trigeminal anaesthesia have been recorded. The best results follow the use of moderately intensive course consisting of courses separated by seven-day intervals of 8, 10 or 12 daily injections of 2 mg. per kg. of body weight; the total amount depending upon individual cases.

It has been used in human **trypanosomiasis** without involvement of the nervous system in Nigeria and has been found as effective as suramin. Mild cases received an average total dasage of 8.8 mg. per kilo. Several cases of death occurred in the Soudan after its use in leishmaniasis and it has been found that solutions exposed to light became toxic and was due to 4-4-diamido-phenyl-benzene carbinol. The solution therefore should be made *fresh* daily and should be neutral or faintly acid.

Since both in leishmaniasis and multiple myeloma there is high serum globulin, stilbamidine has been tried in the treatment of **myelomatosis** in doses 50 to 100 mg. (3/4 to 1½ gr.) intravenously daily till 1000 to 2000 mg. (15 to 30 grs.) have been given when there is a striking relief of bone pain. Neither stilbamidine nor propamidine prolongs the life or alters the course of the disease. It is not safe to use these drugs which are still in experimental stage.

Pentamidine (4-4-diamidino-diphenoxypentane). **Dose.**—1½ grs. or 100 mg. up to a maximum of 2 to 3 grm. It has also been used in trypanosomiasis. It only checks the disease but does not cure it.

Propamidine. **Syn.**—M. & B. 782.—*a* : *w*-(4 : 4′-Diamidino-diphenoxy) propane.—It is useful in trypanosomiasis and kala-azar. Also possesses bacteriostatic but not bactericidal activity against *Staph. aureus* and *B. haemolytic streptococcus*, and this effect is not antagonised by *p*-aminobenzoic acid, pus and tissue fluids. It is therefore useful for local application. In the form of jelly (0.15 p.c.) it has been used with good results in **septic wounds** and **burns**. The cream prepared with paraffin, water and Lanette wax SX is specially useful in fresh burns. A 0.1 p.c. solution has been found useful in **angular conjunctivitis** due to Morax-Axenfeld diplobacillus, after irrigation with boric lotion.

Class D: Drugs used in Trypanosomiasis (Sleeping Sickness)

These include pentavalent arsenic compounds, *viz.*, **Tryparsamide, Cacodylate** (*see* page 526), **Atoxyl, Stilbamidine** and **Suramin.**

TRYPARSAMIDUM. (Tryparsamid.).—Tryparsamide is sodium *N*-phenylglycineamide-*p*-arsonate. Contains 25.1 to 25.5 p.c. of As.

Characters.—A colourless, crystalline powder. Freely soluble in water.

B. P. Dose.—15 to 30 grs. or 1 to 2 grms. *by subcutaneous, intramuscular or intravenous injection.*

Official Preparation

1. **Injectio Tryparsamidi.**—B. P. Dose.—15 to 30 grs. or 1 to 2 grms. by subcutaneous, intramuscular or intravenous injection.

Action and Uses

Tryparsamide causes disappearance of the human trypanosomes from the peripheral blood, specially the

Gambiense infection but the effect on *T. rhodesiense* is not much. The usual dose is 0.3 to 3.0 grms. weekly in 10 p. c. solution intramuscularly or intravenously for eight to ten weeks to be repeated after ten months. For children the dose should be 1 gr. (60 mg.) and for adults, 3/5 gr. (40 mg.) per kilo of body weight. The optimum dose is about 80 mg. per kilo of body weight. A total dosage of 24 grms. is as a rule necessary. During the second stage with nervous symptoms it produces marked improvement in the cell content of the cerebro-spinal fluid with arrest of the symptoms. In this stage the same number of injections are given but the dose is larger, *i. e.* $1\frac{1}{2}$ gr. (100 mg.) for children, $1\frac{1}{8}$ gr. (70 mg.) for young adults, and 0.06 grm. per kilo of body weight for adults. Van den Branden and his colleagues, in the Belgian Congo, advise a total of 20 to 40 grms. in early cases ; and 50 to 100 grms. in chronic ones, in doses of 3 grms ; and 0.5 to 2 grms. for children. Children tolerate the drug well, almost an adult dose. Apart from occasional cases of erythema and very rarely exfoliative dermatitis, the only toxic reaction commonly seen is optic atrophy and blindness. For its action in neurosyphilis *see* page 531.

Sodii Aminarsonas. (Not official). *Syn.—Atoxyl* ; *Soamin.*—Both soamin and atoxyl which are closely allied preparations were first tried in the treatment of **sleeping sickness**; the former extensively than the latter. They both cause the trypanosomes to disappear from the peripheral blood for long periods. They were however found to be of little value in the sleeping stage as they do not penetrate the meninges.

A number of cases of recovery in the early stages have been recorded by different observers. The method of treatment is to give injections of either soamin or atoxyl in 10 p. c. solutions once a week. The usual dose being 3 to 7 grs., commencing with 3 grs. and then working up to 7 grs. The only disadvantage is that it may cause dimness of vision and optic atrophy. The sight therefore requires to be tested during the course of treatment and any restriction in the field of vision necessitates either stoppage of the treatment or reduction of the dose. The routine method is either to give the injection every 5 or 6 days or once a week for a month, or till 100 grs. have been given and then to wait for one month before another course is given. This is continued for at least one year after all signs of the disease have disappeared. (*See* also page 526).

Neocryl. (Not official). *Syn.*—Sodium succinanilomethylamide-*p*-arsonate. A white crystalline substance, readily soluble in water.

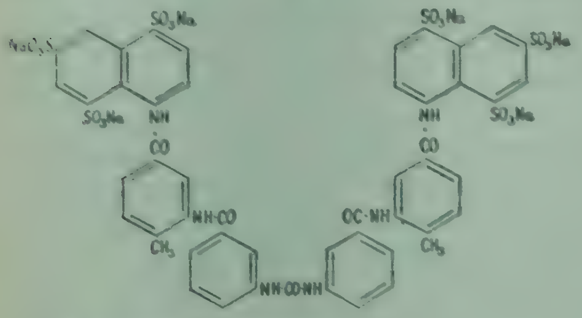
Dose.—1 to 3 grms. or 15 to 45 grs. in weekly doses, intravenously in 15 to 20 p.c. solution in sterile water.

Action and Uses.—It has been used in the treatment of trypanosomiasis and syphilis. In trypanosomiasis when given in the first-stage cases it produces definite clinical improvement, results comparing favourably with those obtained by tryparsamide. In the second-stage cases, the results are not satisfactory.

Neocryl produces definite results in primary, secondary and tertiary syphilis, and has given very satisfactory results in neurosyphilis. In the primary stage it is best combined with bismuth.

SURAMINUM. (Suramin.). **Syn.**—Germanin; Bayer "205"; Moranyl; Antrypol; Fourneau 309.

Suramin is the symmetrical urea of the sodium salt of *m*-benzoyl-*m*-amino-*p*-methylbenzoyl-1-amino-naphthalene-4 : 6 : 8-trisulphonic acid.



$C_{51}H_{34}O_{23}N_6S_6Na_6$

Characters.—A white or pinkish-white or faintly cream coloured powder; odourless; taste, alkaline and slightly bitter. *Soluble* at 20°, in less than 1 part of water; almost insoluble in alcohol (95 p.c.); insoluble in solvent ether, in chloroform and in benzene.

B. P. Dose.—15 to 30 grs. or 1 to 2 grms. by intravenous injection.

Official Preparation

1. **Injectio Suramini.**—**B. P. Dose.**—By intravenous injection: 15 to 30 grs. or 1 to 2 grms. N.B. Dissolve the contents of a sealed container in the required amount of water for injection immediately before use.

Action and Uses.—Its action in **trypanosomiasis** was established by giving injections of the drug to infected small animals chiefly mice; and it has since been extensively used on human beings. It is of great value in the early stage before the central nervous system is attacked because the drug does not penetrate easily the central nervous system. The results were not very encouraging except in infections with *T. rhodesiense*. As a prophylactic it has been found rather effective, a dose of 2 grms. (30 grs.) giving protection for three months or longer. For curative purpose it is given in 1 grm. doses intravenously weekly for 5 to 10 weeks in freshly prepared 10 p.c. solution in distilled water. The total amount necessary to effect a cure is 10 grms. although the trypanosomes usually disappear after 5 grms. Its use is generally supplemented by the administration of tryparsamide, but it has been found that this increases the danger to sight from tryparsamide.

Toxic effects are few, they are chiefly vomiting, skin rashes, peripheral neuritis and irritation of the kidneys leading to nephritis. and dimness of vision.

Class E: Drugs used in Amoebic Infection

These include **Emetine** (see page 336) **Acetarsol, Carbarsone, Aureomycin** (*q.v.*), **Chiniofonum, Quiniodochlorum, Diodoquin, Rivanol, Kurchi Bark** (*q.v.*).

ACETARSOL. **Syn.**—Acetarsone; "Stovarsol"

Source.—Acetarsol is 3-acetylamino-4-hydroxyphenylarsonic acid. Contains 27.0 to 27.4 p.c. of As.

Characters.—A white crystalline powder. Almost *insoluble* in cold water; moderately soluble in boiling water; insoluble in alcohol (95 p.c.); soluble in dilute alkalies.

B. P. Dose.—1 to 4 grs. or 60 to 250 mg.

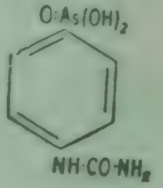
Action and Uses

Acetarsol is therapeutically active when given by the mouth and has been used with some success in chronic amoebic dysentery, specially in the resisting cyst-passing cases. It is generally given by the mouth in 4 gr. doses twice a day after meals for ten days, which form a course.

The second course should be repeated after a rest of one week or better still two weeks. It is also given after a course of emetine to prevent relapse, but often fails to prevent this. It is used in lambliasis, treatment being given for one week. It has been tried in yaws, syphilis, trypanosomiasis and filarial infections but the results were not encouraging.

Its only disadvantage is that it has a tendency to induce dermatitis. A few cases of death are on record, therefore it should be used with caution.

CARBARSONUM. (Carbarson.).—Carbarsone is *p*-carbamido-phenylarsonic acid. Contains 28.1 to 28.8 p.c. of As.



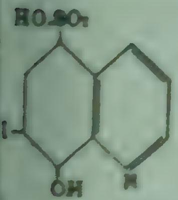
Characters.—A white powder ; almost odourless ; taste, slightly acid. Slightly *soluble* in water, and in alcohol ; nearly insoluble in chloroform and in solvent ether. Soluble in solutions of alkali hydroxides and carbonates.

B. P. Dose.—2 to 3 grs. or 0.12 to 0.2 grm.

ACTION AND USES.—Carbarsone is extolled as a valuable remedy in amoebic dysentery and is non-toxic. It is administered by the mouth in 0.25 grm. or 4 gr. doses in capsules twice a day for 10 days. Although practically insoluble in water it may be dissolved in alkaline aqueous solutions and is readily absorbed after oral administration and can be given for prolonged period without eliciting any toxic effect. It does not produce any nausea or vomiting. In obstinate cases an enema of 2 grms. (30 grs.) in 200 mils (7 ozs.) of warm 2 p.c. sodium bicarbonate solution is instilled into the rectum after a cleansing enema, and repeated every alternate night for five nights. Serious untoward effects are rare, but skin rashes and abdominal pain may occur.

It is contra-indicated where the kidneys and the liver are damaged.

CHINIOFONUM. (Chiniofon.). Chiniofon. Syn.—Pulvis Chiniofoni ; "Quinoxyl" ; "Yatren."—It is a mixture of approximately four parts by weight of 7-iodo-8-hydroxyquinoline-5-sulphonic acid and one part by weight of sodium bicarbonate. Contains 27.5 to 29.6 p.c. of I, and 18 to 22 p.c. of $NaHCO_3$.



Characters.—A light yellow powder ; odourless ; taste, bitter with a sweetish after taste. *Soluble* with effervescence in about 25 parts of water ; insoluble in alcohol (95 p.c.), in solvent ether, and in chloroform.

Note.—Solutions are decomposed by boiling.

B. P. Dose.—1 to 8 grs. or 60 to 500 mg. ***By rectal injection*** **:—15 to 75 grs. or 1 to 5 grms.**

ACTION AND USES

Chiniofon is a relative of quinine and is bitter. Because of its iodine content it is an **antiseptic** and may be used for washing the bladder and vagina, and as a mouth wash in 2 to 3 p.c. solution.

Its chief use is in the treatment of **amoebiasis** i which condition it is administered both orally and also b rectal injection. As it is decomposed by the gastric juice i is given in enteric-coated pills in 4 gr. doses, three times day for one week. Its use should be stopped for 8 or 1 days before it is again repeated. It has the disadvantag of producing diarrhoea. In the form of retention enem it is given in 2½ p.c. solution, when it helps to heal th ulcers wherever it comes in contact with them in th rectum or lower sigmoid. About 200 mils (7 ozs.) bein slowly thrown up the rectum by means of a funnel an tube and retained for 6 to 8 hours. This may be give several times a day at the beginning, subsequently only onc a day. This enema is usually preceded by a rectal was with 2 p.c. bicarbonate of soda. In refractory cases 5 p.c solution may be used without any disagreeable effects. I is especially effective in cases resistant to emetine-bismuth iodide. Manson-Bahr recommends retention enema o chiniofon by day and emetine-bismuth-iodide by night, an continued for 10 to 12 days. It is not a specific but valuable adjunct to other treatment, and is often give after a course of emetine injection or alternately wit emetine-bismuth-iodide in amoebic dysentery. It has als been used in bacillary dysentery and lamblial cysts.

Quiniodochlorum, I.P.L. **Syn.**—Entero-Quinol ; Entero Vioform —Chloro-iodo-hydroxyquinoline may be obtained by iodination o 5-chloro-8-hydroxyquinoline and repeatedly crystallising the produc from hot glacial acetic acid. Contains from 37.5 to 41.5 p.c. iodin and 11.5 to 12.2 p.c. chlorine. It has been used in amoebiasis, bacil lary dysentery and colitis with much success.

Characters.—Greyish-yellow powder. Odour, faintly aromatic. Almost inso luble in water sparingly soluble in alcohol (90 p.c.), soluble in hot glacial aceti acid.

Dose.—4 grs. or 0.25 grm. in tablets twice daily for ten days. The cours being repeated after a week's rest. Total quantity being 15 grms.

Diodoquin. (Not official).—5, 7-Diiodo-8-hydroxyquinoline.—I contains much higher proportion of iodine (63 p.c.) than chiniofonum and is used in the treatment of **amoebic** dysentery. In fact it is th drug of choice in amoebiasis. It has the advantage in not causin diarrhoea. It is almost non-toxic, but in some cases may give ris to pruritus ani. For routine treatment tablets of 3.2 gr. each ar given three times daily for 20 days.

Rivanol. (*Not official*). *Syn.—Ethoxy-diamino-acridine lactat* —A yellow dye-stuff with powerful antiseptic action. Useful i human amoebiasis, bacillary dysentery and acute and chronic ente ritis of adults and children.

Dose.—25 mg. or 2/5 gr. for adults ; 8 mg. or 1/8 gr. for children, 3 to times a day. May also be used as enema, 10 to 20 ozs. of 1 in 5000 to 1 in 300 solution injected slowly.

CLASS F : Drugs used in Bacterial Invasion (Systemic Anti-infectives)

Till recently sterilisation of the blood stream agains some bacterial invasion was looked upon as an unattainabl ideal, but the introduction of the drugs of this group ha

altered the situation. In 1935 Domagk found that sulphamidochrysoidin will cure an otherwise fatal streptococcus infection in mice. This compound was placed in the market under the name of 'prontosil'. And it has been found that this drug when given to a patient will differentiate between the protoplasm of the bacteria and that of the man, and will attack the bacteria leaving the tissues of the host more or less uninjured. Later it was found that its activity was due to the liberation of *p*-aminobenzenesulphonamide (sulphanilamide), a compound prepared as early as 1908 by Gelmo of Vienna.

1. Sulphonamide Group

SULPHANILAMIDUM

(Sulphanilamid.)

Syn.—Prontosil Album ; Sulphonamide P ; Streptocide ; Prontylin ; Colsulanyde ; Sulfanil.

Source.—Sulphanilamide is *p*-aminobenzenesulphonamide and may be prepared by the hydrolysis of the amide of acetylsulphanilic acid with hydrochloric acid, followed by decomposition of the resulting hydrochloride with alkali.

Characters. Colourless crystals or a white crystalline powder ; odourless ; taste, slightly bitter with a sweet after taste. *Soluble* in 250 parts of water at 15.5°C. ; in 170 parts of water at 20°C. ; in 115 parts of water at 25°C. ; sparingly soluble in alcohol (95 p.c.). Insoluble in solvent ether, in chloroform and in benzene

B. P. Dose. *Initial dose* :—30 grs. (2 grm.). *Subsequent doses* :—15 grs. (1 grm.) every four hours.

The structure of the sulphonamides is based primarily on the benzene ring  *i.e.* (C_6H_6). By replacing one of the hydrogens by an amine group ($-NH_2$), aminobenzene  NH_2 *i.e.* aniline is formed. By attaching one sulphonamide group (SO_2NH_2) to the *para* position of aminobenzene, *para*-aminobenzene-sulphonamide is formed, H_2NO_2S  NH_2 shortly known as "sulphanilamide". the mother substance of all the other derivatives.

SULPHACETAMIDUM. (Sulphacetamid.). **Syn.—Albucid.**—Sulphacetamide is *p*-aminobenzenesulphonacetamide.

Characters.—A white, or yellowish-white, crystalline powder ; odourless ; taste, acid and slightly saline. *Soluble* in 150 of water at 20°C., and in 15 of alcohol (95 p.c.) ; insoluble in solvent ether ; soluble in acids and in solutions of alkali carbonates.

NH_2  $SO_2NH.OC.CH_3$

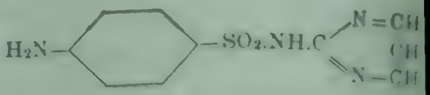
Sulphacetamidum Sodium. Syn.—Soluble Sulphacetamide.—Sulphacetamide Sodium is sodium *p*-aminobenzenesulphonacetamide.

Characters.—A white, or yellowish-white, microcrystalline powder ; odourless ; taste, slightly bitter. *Soluble* in 1.5 parts of water ; sparingly soluble in alcohol (95 p.c.).

Non-official Preparation

Guttae Sulphacetamidi Fortes and Mites, B.P.C. The strong eye-drops contain sodium sulphacetamide [illegible] p.c. and the weak eye drops conatin 10.0 p.c. with boric acid and distilled water.

SULPHADIAZINA. (Sulphadiazin.).—Sulphadiazine is 2-(*p*-aminobenzenesulphonamido)-pyrimidine.



Characters.—A white, or yellowish-white powder, slowly darkening on exposure to light ; almost odourless and tasteless. *Soluble* in about 13,000 parts of water, sparingly soluble in alcohol (95 p. c.) and in acetone ; readily soluble in dilute mineral acids and in aqueous solutions of alkali hydroxides.

B. P. Dose.—*Initial dose.*—**30 grs. (2 grms.).** *Subsequent doses.*—**15 grs. (1 grm.) every four hours.**

Official Preparation

1. **Tabellae Sulphadiazinae.—B. P. Dose.**—*Initial dose.*—**30 grs. (2 grms.)** *Subsequent doses.*—**15 grs. (1 grm.) every four hours.**

Sulphadiazina Sodium. Syn.—Soluble Sulphadiazine.—Sulphadiazine Sodium is the sodium derivative of 2-(*p*-aminobenzenesulphonamido)-pyrimidine.

Characters.—A white, or yellowish-white powder ; odourless : almost tasteless *Soluble* **in 2 parts of water ; sparingly soluble in alcohol (95 p.c.).**

B. P. Dose.—*Initial dose* :—**30 grs. (2 grms.).** *Subsequent doses* :—**15 grs. (1 grm.).** *By intravenous injection* :—**8 to 30 grs. (0.5 to 2 grms.).**

Official Preparation

1. **Injectio Sulphadiazinae Sodii.—B. P. Dose.—By** intravenous injection :—**8 to 30 grs. or 0.5 to 2 grms.**

SULPHATHIAZOLUM. (Sulphathiazol.). Syn.—Thiazamide (M. & B. 760) ; Cibazol.—Sulphathiazole is 2-(*p*-aminobenzenesulphonamido)-thiazole.

Characters.—A white, or yellowish-white powder ; odourless ; almost tasteless. *Soluble* in about 2500 parts of water, slightly soluble in alcohol (95 p.c.), soluble in dilute mineral acids and in solutions of alkali hydroxides and carbonates.

B. P. Dose.—*Initial dose* :—**30 grs. (2 grms.).** *Subsequent doses* :—**15 grs. (1 grm.) every four hours.**

Official Preparation

1. **Tabellae Sulphathiazoli.—B. P. Dose.**—*Initial dose* :—**30 grs. (2 grms.).** *Subsequent doses* :—**15 grs. (1 grm.) every four hours.**

Sulphathiazolum Sodium. Syn.—Soluble Sulphathiazole : Thiazamide Sodium.—Sulphathiazole Sodium is the pentahydrate of the sodium derivative of 2-(*p*-aminobenzenesulphonamido)-thiazole.

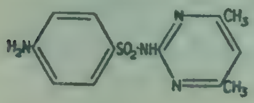
Characters.—A white, or yellowish-white, microcrystalline powder, odourless : almost tasteless. *Soluble* in about 3 parts of water, and in 20 parts of alcohol (95 p. c.).

B. P. Dose.—*Initial dose* :—30 grs. (2 grms.). *Subsequent doses* :—15 grs. (1 grm.) every four hours. *By intravenous injection* :—**8 to 30 grs (0.5 to 2 grms.).**

Official Preparation

1. **Injectio Sulphathiazoli Sodii.—B. P. Dose.—8 to 30 grs.** or **0.5 to 2 grms.** by *intravenous injection.*

SULPHADIMIDINA. Syn.—Sulphamethazine: Sulphamezathine.—Sulphadimidine is 2-(*p*-aminobenzenesulphonamido)-4 : 6-dimethylpyramidine.



Characters.—A white or creamy-white powder : odourless or almost odourless ; taste, bitter. Almost *insoluble* in water and alcohol (95 p.c.) ; *soluble* in dilute mineral acids and in aqueous solutions of alkali hydroxides.

B. P. Dose.—*Initial dose* :—**30 gr. or 2 grm.** *Subsequent doses* :—**15 gr. or 1 grm. every six hours.**

Official Preparation

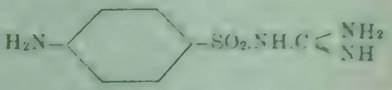
1. **Tabellae Sulphadimidinae.—B. P. Dose.**—*Initial dose* :—**30 gr.** or **2 grm.** *Subsequent doses* :—**15 gr. or 1 grm. every six hours.**

Sulphadimidina Sodium.—Sulphadimidine Sodium is the sodium derivative of 2-(*p*-aminobenzenesulphonamido)-4 : 6-dimethylpyrimidine.

Characters.—A white or creamy-white powder ; odourless ; taste, bitter and alkaline. *Soluble* in about 2.5 parts of water ; sparingly soluble in alcohol (95 p.c.).

B. P. Dose.—*By intravenous injection* :—15 to 30 gr. or 1 to 2 grm.

SULPHAGUANIDINA. (Sulphaguanidin.).—Sulphaguanidine is *p*-aminobenzenesulphonylguanidine monohydrate.



Characters.—A white, needle-like crystalline powder, which slowly darkens on exposure to light ; almost odourless, and tasteless. *Soluble* in about 1000 parts of water at 25° and in about 10 parts at 100° C. ; readily soluble in dilute mineral acids, and insoluble in aqueous solutions of alkali hydroxides.

B. P. Dose.—30 to 60 grs. or 2 to 4 grms.

Official Preparation

1. **Tabellae Sulphaguanidinae.—B. P. Dose.—30 to 60 grs. or 2 to 4 grms.**

SUCCINYLSULPHATHIAZOLUM. Syn.—Sulphasuxidine.—Succinylsulphathiazole is *p*-2′-sulphonthiazolylamidosuccinanilic acid.

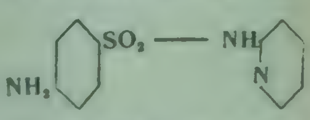
Characters.—A white or yellowish-white, crystalline powder ; odourless ; stable in air ; slowly darkens on exposure to light. Very slightly *soluble* in water ; sparingly soluble in alcohol (95 p. c.) ; insoluble in chloroform ; soluble in solutions of alkali hydroxides in water.

B. P. Dose.—45 to 90 grs. or 3 to 6 grms.

Official Preparation

1. **Tabellae Succinylsulphathiazoli.—B. P. Dose.—45 to 90 grs. or 3 to 6 grms.**

SULPHAPYRIDINA. (Sulphapyridin.). **B. P. C. Syn.—Dagenan; M. & B. 693.—Sulphapyridine is 2-**(*p*-aminobenzenesulphonamido)-pyridine.



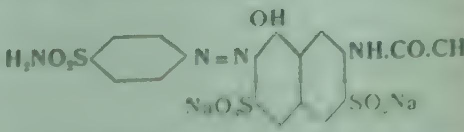
Characters.—White, or yellowish-white crystals or crystalline powder, which slowly darkens on exposure to light ; odourless ; taste, very slightly bitter. *Soluble* in 3000 parts of water, at 20°, in 100 parts of boiling water, in 400 parts of alcohol (95 p. c.), in dilute mineral acids and in aqueous solutions of alkali hydroxides.

Dose.—*Initial dose* :—60 gr. or 4 grm. *Subsequent doses* :—15 gr. or 1 grm.

Non-official Preparations

1. **Prontosil Rubrum.** *Syn.—Sulphamidochrysoidin.*—The hydrochloride of 4′-sulphamido-2 : 4-diaminoazobenzene. A red crystalline powder ; soluble in 400 parts of water. Dose. 0.5 grm. (8 grs.) in tablets. It is the original preparation.

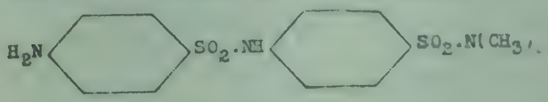
2. **Prontosil Soluble.** *Syn.—Neo-prontosil* ; *Streptozon-S.*—The disodium salt of sulphanilamide-azo-hydroxy-acetylamino-naphthalene-disulphonic acid. Soluble 1 in [illegible] of water. **Dose.**—[illegible] to 10 mils daily by intramuscular injection. Supplied in ampoules containing 5 and 10 mils of [illegible] and [illegible] p. c. solution for intramuscular injection.



3. **Soluseptasine.** It is disodium-*p*-benzene-sulphonamide. Said to be less toxic than sulphanilamide. Dose.—[illegible] to [illegible] mils of a 5 or 10 p. c. solution subcutaneously, intramuscularly or intravenously.

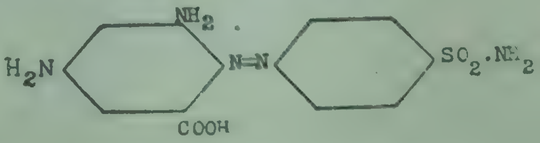
4. **Proseptasine.** *Syn.*—M and B 125.—It is *p*-benzyl-aminobenzenesulphonamide. **Dose.**—0.5 grm. (8 grs.) in tablets *by mouth*. Toxicity is negligible and larger doses can be given with safety.

5. **Uleron.** *Syn.—Diseptal A.*—It is dimethyl derivative of sulphanilamide.

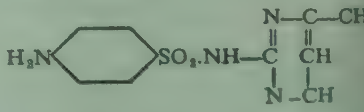


A colourless substance with a slightly bitter taste. Insoluble in water, slightly soluble in alkali and acetone **Dose.**—7½ to 15 grs. or 0.5 to 1 grm. thrice daily after meals. Children half the dose.

6. **Rubiazol.**—It is 6-carboxy-4-sulphamido-2′-4′-diaminoazobenzene, and differs from prontosil in possessing a COOH group. **Dose.**—0.2 grm. (3 grs.) by the mouth. Intramuscularly in doses of 5 mils of a 5 p. c. solution.



7. **Sulphamerazine.**—It is 2-(*p*-aminobenzenesulphonamido)-4-methylpyrimidine, a monomethyl derivative of sulphapyrimidine (sulphadiazine).



Characters.—White, crystalline powder ; very poorly *soluble* in water, readily soluble in dilute acids and alkalies. The sodium salt is soluble in water.

Dose.—45 to 60 grs. or 3 to 4 grms. (initial dose), followed by 15 grs. or 1 grm. maintenance dose.

8. **Phthalylsulphathiazole.** *Syn.—Sulphathalidine.*—2-(N⁴-phthalyl-sulphanilamide) thiazole.—Valuable intestinal antiseptic.

Dose.—3 to 8 grms. (45 to 120 grs.) in divided doses daily.

All these compounds fall into three groups, viz.—

Class I. These are formed by replacing one of the hydrogen atoms of sulphonamide (SO_2NH_2) group. They are sulphapyridine, sulphathiazole, sulphadiazine, sulphacetamide, sulphadimidine, sulphamerazine. These are not converted into sulphanilamide and are superior in their effect to the parent substance.

Class II. These are formed by replacing one of the hydrogen atoms of the amino group (NH_2). These are prontosil, rubiazol, proseptasine, etc. These compounds are either converted or partially hydrolysed into amino-benzene sulphonamide (sulphanilamide) and are not more efficacious than the parent compound, namely sulphanilamide.

Class III. These are very poorly absorbed from the gastro-intestinal tract, and are largely used in bacterial infections of the intestinal tract. They are sulphaguanidine, sulphasuxidine and sulphathalidine.

PHARMACOLOGY

Sulphanilamide in doses higher than those used therapeutically has not effect on the smooth muscles, heart, blood pressure, respiration or the basal metabolism. It is therefore physiologically inert. Toxic effects noticed in experimental animals are referable chiefly to the central nervous system. These are ataxia, rigidity, convulsions and at times coma.

Mechanism of action.—Some correlation exists between the chemical structure and therapeutic activity of these compounds *in vivo.* Thus it has been found essential that the amino (NH_2) group in the benzene ring should be linked with the sulphonamide (NH_2SO_2) group in the *para* position ; and any attempt to alter the position to *ortho* or *meta* position destroys the activity. It is believed that the resemblance of sulphanilamide structure to *p*-aminobenzoic acid is possibly one of the factors essential for its anti-infective property. The "ortho" or "meta" derivatives do not enjoy this relationship to PABA.

Various views have been advanced to explain the mechanism of the action of these drugs. Since prontosil is excreted as sulphanilamide in the urine, it has been suggested that *para*-aminobenzenesulphonamide is responsible for its activity in the body. Although the majority of workers subscribe to this view, yet on the Continent it is held that prontosil *per se* may have some activity in the tissues, or that it may be converted into some substance other than sulphanilamide. Compounds like sulphapyridine, sulphathiazole, sulphadiazine, etc., act in their original form, whereas others like prontosil, depend for their activity on the formation of either sulphanilamide or some other compound in the body.

These drugs act on the bacteria themselves, and either prevent their growth (bacteriostatic) or act as germicides (bactericide). The sulphonamide-susceptible bacteria are acted on only when they are multiplying. There is therefore a 'lag' phenomenon in its activity.

In some cases the drug attaches itself to the surface layer of the invading organism thus interfering with its normal activities. In others it unites with some vital enzyme system of the bacteria. It is now recognised that *para*-aminobenzoic acid (known as PABA) is an essential growth substance of many bacteria and that in the enzyme reaction necessary for the utilisation of *para*-aminobenzoic acid by the cell, *para*-aminobenzenesulphonamide (sulphanilamide) offers competition for a position in this reaction because of the similarity between the chemical structure of the two compounds. If sufficient sulphanilamide is present to displace *para*-aminobenzoic acid from the enzymic reaction, the growth of the bacterial cell is inhibited by substrate competition ; so that the bacteria are reduced in number and weakend and are readily destroyed by phagocytes and other antibodies present in the blood. If however an excess of *para*-aminobenzoic acid is present sulphanilamide is displaced and growth is unimpeded.

These compounds do not help development of immunity, so that when the treatment is stopped there is the possibility of a relapse. Moreover, by stopping the acti-

vity of the infective organisms they may hinder formation of immunity in the body leaving the patient with a latent infection without the means to combat it.

Antagonism and Synergism.—The bacteriostatic action of sulphonamides is antagonised by pus, protein breakdown products, extracts of micro-organisms and by necrotic tissues. This antagonism is probably due to *p*-aminobenzoic acid. Some local anaesthetics which contain *p*-aminobenzoic acid are powerful antagonists and should be avoided when these drugs are used (*see* page 272). Alcohol increases the cerebral effects and barbiturates increase toxicity. Ether and chloroform have no special effect either in increasing or diminishing toxic manifestations. Severe reactions follow use of saline purgatives, possibly due to formation of sulphaemoglobin.

Resistant strains and sensitisation.—It has been observed that a strain of an organism normally sensitive becomes less sensitive or even resistant. This happens not only in cultures but also in patients, and has been attributed to the increasing capacity of the bacteria to synthesize *p*-aminobenzoic acid. Therefore it has been suggested that the organism should at the beginning be overwhelmed with full doses and thus prevent from becoming resistant. It has also been observed that when small doses have been used the patients become sensitised to these drugs which if allowed to develop will prevent the use of these remedies in an emergency. These compounds have no action on anaerobic streptococci or in virus infections.

Specificity.—The different derivatives vary in their activity, and this variation is modified by various factors, such as their rate of absorption and elimination, degree of acetylation, distribution and concentration in the blood and other fluids, etc. Thus sulphanilamide is primarily of value in the treatment of streptococcal infections, especially those of the haemolytic type; sulphapyridine, while of value in most of the infections where the parent substance is used, possesses special action on pneumococcus, gonococcus and meningococcus ; sulphathiazole while having the same chemotherapeutic action of both the compounds is especially effective against *Staph. aureus.*

The reason why some sulphonamides are more active than others and why some are selective in their action, i.e. are specific against certain bacteria was much discussed While some hold that more closely a compound resembles *p*-aminobenzoic acid the more capable will it be of competing with this substance for a specific receptor, and therefore the more active will it be. Others are of the opinion that the activity depends upon the degree of dissociation that a compound undergoes and that the more active sul-

phonamides like sulphadiazine or sulphathiazole owe their greater activity to their greater degree of ionization. Therefore the more active compounds affect a larger number of bacteria, while the less active ones have a bacteriostatic action only.

Absorption, Distribution, Fate and Clearance

Absorption.—Sulphonamides when administered by the mouth are quickly *absorbed* (except succinylsulphathiazole, sulphaguanidine and phthalylsulphathiazole) mainly from the upper part of the intestine, although some may be absorbed from the stomach. Subcutaneous injection does not lead to a higher concentration in the blood than does oral administration, while after intravenous injection the rate of elimination is the same as after oral use. Absorption is quicker when it is given in solution and in empty stomach than when given after meals and in tablets or capsules. Alkalies hasten absorption.

Sulphanilamide is more soluble and is absorbed within 4 to 12 hours ; next in order of solubility and absorption comes sulphathiazole, while the absorption of sulphapyridine is slower still, less regular and less complete. Succinylsulphathiazole and phthalylsulphathiazole are sparingly soluble in water and are very poorly absorbed, only about 5 p.c. being detected in the urine but are excreted with the stool in high concentration. All soluble compounds however are not readily absorbed. Thus sulphaguanidine, though comparatively more soluble, is very poorly absorbed and therefore remains in the colon to exert its bacteriostatic effect there ; while sulphadiazine though poorly soluble than any of the above compounds, is fairly readily absorbed. Sulphamerazine is more quickly absorbed than sulphadiazine and more slowly excreted than sulphadimidine.

The soluble preparations like the sodium salts are absorbed and excreted rapidly. It is therefore necessary to administer these drugs at more frequent intervals to maintain an efficient concentration.

These drugs are poorly absorbed by the rectum ; when a sodium salt is used absorption through this channel is slightly better. Sulphadiazine and sulphapyridine are poorly absorbed from the large intestine.

The *concentration* in the blood is regarded as a valuable guide to the efficiency of treatment although in some cases they may be effective in concentrations much below those regarded as therapeutic. The concentration depends upon the absorption and excretion. After a dose of 2 grms. to an average adult, maximal concentration of 2 mg. per 100 mils of blood is reached in four hours, then it falls gradually to zero during the following 24 hours when the

excretion is complete. The optimum blood concentration to be effective is 4 to 15 mg. per 100 mils and this depends upon the severity of the infection and on the particular drug used. To maintain a uniformly high concentration it is necessary to *use the drug every four hours day and night.*

Distribution.—On entering the blood sulphanilamide quickly penetrates all the fluids and tissues of the body. In addition to normal body fluids, such as saliva, milk, sweat, tear, etc., it is also found in pathological exudates, *e.g.* in pleural effusion. It passes readily into foetal blood and amniotic fluid. In the cerebro-spinal fluid its concentration is about 75 p.c. of that in the blood and the drug appears to pass as readily into the cerebro-spinal fluid of the patients suffering from meningitis as that of healthy subjects.

The distribution of sulphanilamide is more uniform than other compounds. Sulphapyridine resembles sulphanilamide in its power of ready penetration in concentrations not far removed from that of the blood, but unlike the latter it is present in higher concentration in the liver than in other tissues. Prontosil soluble passes very slowly from the blood to the cerebro-spinal fluid and perhaps little or none of uleron or proseptasine. Sulphathiazole resembles sulphapyridine in its distribution except that its penetration to spinal fluid is poor. Sulphadiazine resembles more sulphapyridine than sulphathiazole, its concentration in the spinal fluid is about 50 p.c. of that in the blood.

Sulphanilamide concentrates more in the red blood cells than in the plasma ; the concentration of sulphapyridine is the same in both the red blood cells and plasma ; sulphathiazole is found in greater concentration in the plasma. All are found in higher concentration in the liver than in the blood and least in the spleen.

Fate.—After absorption much of the sulphonamide is conjugated, especially with acetate, in the liver by replacement of one H-atom of the amino group with an acetyl group ($COOCH_3$) known as *acetylation.* This acetylated or conjugated form is therapeutically inert, but equal in toxicity to the original sulphonamide, fortunately it is excreted very rapidly. Of the total amount of drug circulating in the blood, between 10 to 15 p.c. of sulphanilamide, and up to 60 to 75 p.c. of sulphapyridine become acetylated. The acetylation of sulphathiazole is less than sulphapyridine under the same conditions. Of all the sulphonamides, sulphadiazine is least acetylated (10 p.c.) and there is less tendency to form uroliths as the conjugated drug is more soluble in the urine than the free portion, whereas acetylsulphapyridine being less soluble than the free drug preci-

pitates out, causing formation of crystals resulting in haematuria, renal colic or obstruction.

Clearance.—Sulphanilamide is chiefly *excreted* by the kidneys both in free and conjugated forms, entirely by glomerular filtration. The amount excreted through other routes is comparatively insignificant. Of the drug in the glomerular filtrate 70 to 80 p.c. is reabsorbed by the tubules ; diuresis will thus favour excretion of the drug and a state of impaired renal function will have the opposite effect. After a single dose the excretion is complete between 48 to 72 hours. After the same period with repeated doses a state of equilibrium is obtained between the amount of drug taken and the amount eliminated.

Over 90 p.c. of sulphanilamide, of which 25 to 50 p.c. in the conjugated form, is excreted in the urine. Sulphapyridine is excreted largely in the acetylated form with the urine but less than sulphanilamide. Sulphathiazole is excreted almost entirely by the kidney very rapidly. Because of this it is very difficult to maintain adequate concentration in the blood even when administration is adequate. Excretion of sulphadiazine is slower than others and takes 48 to 72 hours for complete elimination. Owing to very slow absorption, only about 5 p.c. or less of the total dose of succinylsulphathiazole is excreted in the urine.

They appear in the *bile* in concentrations about the same as those in the blood. Although acetylation takes place in the liver not much of the derivative appears in the bile. They are also found in the *milk* and in the *tears* in very small quantities.

Toxic Manifestations

Ehrlich's observation that one must be prepared to run certain risk in order to do effective chemotherapy holds good with regard to these compounds which are liable to give rise to certain toxic manifestations. These reactions arise either from toxicity of the drugs or from hypersensitiveness of the patient. They may affect (*a*) *the nervous system* causing mental disturbances, giddiness, palpitation, headache, optic neuritis, and peripheral neuritis ; (*b*) *the skin*, giving rise to various skin rashes and exfoliative dermatitis ; (*c*) *the haemopoietic system*, producing leucopenia, agranulocytosis, acute haemolytic anaemia and thrombocytopenia ; (*d*) *urinary system*, causing acute nephritis, haematuria, pain in flank, albuminuria, even anuria ; (*e*) *digestive system*, causing nausea, vomiting diarrhoea, acute hepatitis or even yellow atrophy of the liver ; (*f*) *cyanosis*, *methaemoglobinaemia*, *sulphaemoglobinaemia*, excessive porphyrin formation.

Symptoms like vertigo, nausea, mild vomiting, slight cyanosis do not as a rule demand stoppage of the drug, but should put the physician on his guard as these are often the precursors of many of the more serious toxic reactions. Persistent cyanosis or dyspnoea, severe vomiting, prostration, skin reaction, hyperpyrexia or subnormal temperature and acidosis are more or less moderately severe symptoms and the physician should use his discretion in stopping further use of these drugs. Agranulocytosis and haemolytic anaemia demand stoppage of treatment.

With the exception of acute leucopenia, almost all the toxic manifestations occurring within the first two weeks can be recognised by careful observation, and whenever possible white cell count, haemoglobin estimation and examination of the urine should be done and the amount of urine passed daily carefully watched. Any sign of oliguria or presence of gross blood in the urine demands forced drinking of water. The temperature should be taken regularly even during the afebrile period to detect the 'drug fever'. It is necessary to enquire whether the patient had any reaction from any of these derivatives during the course of treatment. Should the patient give a history of such reaction, then give a test dose of 0.3 grm. first and observe carefully for twenty-four hours for any sign of reaction and then proceed cautiously.

Cyanosis.—This may be due to formation of some unknown pigment from sulphanilamide in the body. It may also arise from the presence of methaemoglobin or sulphaemoglobin in the red cells. Since the formation of methaemoglobin from haemoglobin is reversible, this can be prevented or abolished by the administration of methylene blue in 2 gr. doses three times a day by the mouth or in bad cases by intravenous injection of 10 to 20 mils of 1 p.c. solution. Sulphaemoglobinaemia, unless associated with symptoms of oxygen want, and in severe anaemic patients, may be ignored. It was thought that the formation of sulphaemoglobinaemia was favoured by the intake of foods containing a high proportion of sulphur, such as eggs. This view has been abandoned and it is now believed that the formation of sulphaemoglobin may be favoured by the breakdown of sulphur-containing compounds in the intestines, and therefore salines and other drastic purgatives, which favour this condition, should be avoided. If a purgative is required give liquid paraffin, or better still begin treatment after a bowel wash. Sulphaemoglobinaemia is however rare with sulphapyridine, sulphathiazole, sulphaguanidine, sulphacetamide and uleron.

Nausea and **vomiting** are more frequent with sulphapyridine and often give trouble. These are avoided by administering the requisite amount in smaller doses at frequent intervals, or as fine powder suspended in milk, or by giving sodium bicarbonate 8 to 15 grs. (0.5 to 1 grm.) and 15 to 30 grs. (1 to 2 grms.) of dextrose in a little water before giving the drug.

Crystalluria.—Sulphonamides and their acetyl derivatives crystallise out when the urine becomes scanty and concentrated giving rise to haematuria, renal pain, oliguria and anuria. The factors responsible are (1) deficient intake of fluid, (2) toxaemia with acidosis, and (3) vomiting, sweating and high temperature. Even sulphaguanidine and sulphasuxidine, regarded safe from this side-effect, can produce it in dehydrated patients. Deposition of crystals in the renal tubules, pelves and lower ureter occurs when the reabsorption of water from the tubules increases the concentration of the drug in the urine, e.g. 170 mg. per 100 mil. This reaction occurs more frequently with sulphapyridine and sulphathiazole. Irrespective of the concentration in the blood, sulphadimidine does not damage the kidney and sulphamerazine is distinctly less harmful than sulphadiazine.

Prevention depends upon maintaining a daily output of urine to 42 to 52 ozs. of alkaline reaction (pH more than 7.5) and a specific gravity below 1,014. An intake of 6 pts. of fluid daily is sufficient. For **crystalluria,** use copious fluids (up to 9 pt.) by the mouth or 5 p. c. glucose with 4.28 p. c. bicarbonate of soda by intravenous drip method. Excessive fluid intravenously may cause overhydration and pulmonary oedema.

Blood Dyscrasias usually occur in those who have received large doses for a long period, for a fortnight or more. There may be anaemia, leucopenia or agranulocytosis.

Leucopenia during the first few days of treatment is of little significance, but when it appears after the tenth day it is dangerous as it may lead to agranulocytosis. Ordinarily no action is necessary except careful observation of the blood unless the number comes down below 4000 and progressive neutropenia appears.

A mild degree of anaemia is common but a progressive form may appears from high dosage. *Acute haemolytic anaemia* may appear 2 to 6 days after treatment and is due to idiosyncrasy. *Haemoglobinaemia* and *haemoglobinuria* may occasionally occur and should be treated with alkalies and plenty of fluid to prevent blocking of renal tubules.

The danger lies in **agranulocytosis**, which may be considered to have appeared when the white cell count comes down to 2,500 and the granulocytes to 1,000. It generally appears 4 to 21 days after commencing treatment and is associated with pyrexia, lassitude, sorethroat and sometime skin rashes and jaundice.

In all these conditions treatment should be stopped and the tissues flushed with fluids and blood transfusion resorted to. For the treatment of agranulocytosis several drugs are now used. They are: penicillin, pyridoxine hydrochloride, folic acid, liver extract, pentose nucleotide.

Sulphonamide **dermatitis** may be due to light sensitiveness, porphyrins being the light sensitising agents. Therefore sun bathing and exposure to ultra-violet rays should be prohibited. This condition is sometimes associated with stomatitis and mental apathy, and porphyrin in the urine. It has therefore been suggested that these **pellagra-like syndrome** could be treated with nicotinic acid. Ascorbic acid 0.5 grm. daily by injection or nicotinic acid 50 mg. by mouth four times daily proved effective also in alleviating unpleasant sequelae and other side-effects. Various types of **skin rashes** have been observed. These appear more often with sulphanilamide and sulphathiazole and less with sulphapyridine. They generally appear about the 8th or 9th day, although may appear any time within 21 days and are seen chiefly on the exposed surface of the skin, or may be generalised. Urticarial, scarlatiniform, purpuric, maculopapular, or **exfoliative dermatitis.**

Effect on acid-base equilibrium.—Sulphonamides tend to cause a shift in the reaction of the body fluids towards the acid side, bicarbonate being lost from the blood. There appears to be a fall in the carbon dioxide-combining power of the plasma with or without signs of acidosis. This was supposed to be due to a primary alkali deficit type of acidosis. Although acidosis does not follow the use of sulphadiazine, sulphathiazole, or sulphapyridine, it is desirable to use alkalies. Administration of sodium bicarbonate or lactate will prevent low CO_2 content of the blood and acidosis and renal injury. Sodium acetate has also been recommended on the idea that the toxicity may be due to the withdrawal of the acetate precursors and lowering of the CO_2 capacity. Besides supplying the alkali, the acetate also supplies the acetyl radicle thus preventing the metabolism of acetate precursors (e.g. glucose).

Drug fever.—A secondary rise of temperature usually seven to eight days after the commencement of the drug treatment is sometimes observed. It is important to distinguish this fever both from recrudescence of the bacterial infection and from fever associated with drug eruption.

Drug sensitivity.—Some persons are specially sensitive to these drugs and even a small single dose will cause giddiness, itching of the skin, oedema of the lips, and erythematous rash. With some, the rash appears at one particular spot every time the drug is taken (fixed eruption).

Therapeutics

At first these drugs were used chiefly in the treatment of streptococcal infections, and the brilliant results which followed their use made the clinicians give these a trial in the treatment of other infections. In fact they were used in infections with *Str. haemolyticus*, *Str. viridans*, *enterococcus*, *Bacterium coli* and other coliform organisms, *Prot. vulgaris*, *gonococcus* and *meningococcus* with good results. With the introduction of newer compounds the field of usefulness of these drugs in other infections has extended. Thus sulphapyridine is specially toxic to *pneumococcus*, and superior to sulphanilamide in meningococcus and gonococcus infections. Sulphaguanidine, sulphathalidine (phthalylsulphathiazole) and succinylsulphathiazole are drugs of choice for Shiga, Flexner and Sonne strains of *dysentery bacillus*. Sulphathiazole again proved to be effective in infections with *Staph. aureus.*

The selection of a particular derivative depends upon various factors, namely, the nature of the infective process, solubility, toxicity, and special sensitiveness of the particular derivative on the infective organism. Although most of the compounds have similar action, some are more effective in a given condition than others. Sulphadiazine and sulphadimidine are favoured because of their low toxicity and because relatively less untoward reactions follow their use. They are of special value in pneumococcus, staphylococcus, menigococcus, streptococcus, etc.

These derivatives are used not only as a curative in **puerperal septicaemia** but also as a preventive before childbirth in patients who may have a septic focus or have been exposed to infection. Similarly, they have yielded good result in **erysipelas** and their use is followed by rapid fall of temperature, at the same time the spread of the disease is cut short with diminished mortality rate.

All these compounds are of great value in **meningitis** and as soon as diagnosis is made clinically no time should be lost in giving the drug and without waiting for bacteriological confirmation.

The Ministry of Health recommends the following :— For the first 2½ to 3 days the daily dosage is : for infants under 2 years, 3 grms. ; from 2 to 5 years, 7½ grms. ; 15 years and over, 9 grms. ; and should be given every 4 hours night and day during the first few days and thereafter, if thought fit, six-hourly. For adults, the first two single doses should not exceed 1½ grms. each, or a total twenty-four hour dose of 9 grms. After the first 2½ to 3 days, the dose may be gradually reduced over the next four to five days, the treatment being completed in from 7 to 9 days.

The above dose is meant for sulphanilamide but sulphadiazine and sulphadimidine may be used with advantage because they are less toxic and untoward reactions rarely follow their use. In case of vomiting one of the soluble preparations may be used by intramuscular injection. From the very commencement of treatment the patient should be made to drink large quantity of fluids at least 3 to 4 pints daily. Both in puerperal septicaemia and meningitis success depends upon securing 10 to 15 mg. concentration of the drug rapidly in the blood.

These compounds have been used with success in septic sore-throat, otitis media, arthritis, etc.

For the treatment of **gonococcal infection** sulphathiazole and sulphadiazine are preferred although sulphacetamide and uleron also posssess special action in this condition. Given in adequate dosage for a sufficient period they will cure 75 p. c. of early cases in the male. The usual method is to give 1 grm. (15 grs.) every four hours, if possible, night and day. This treatment should be continued for five to ten days. If cure is not effected, the treatment should be stopped for a week and after one week a second course of 6 grms. a day may be given for the same period, provided examination of blood shows no leucopenia. If the treatment is confined as above rarely any toxic symptoms are noticed, although there may be headache, nausea or rarely, erythematous rash. These disappear on stoppage of treatment. Severe lumbar pain, haematuria or even agranulocytosis may appear if the treatment is prolonged with larger doses and with less fluid intake.

In chronic cases more prolonged treatment, or repeated course with urethral irrigation are necessary. Uleron in excessive doses may give rise to peripheral neuritis.

The introduction of these drugs has given a new and potent weapon for the treatment of **infections of the urinary tract.** Since the activity of the different preparations varies with the different types of infections, it is desirable that the urine is examined bacteriologically so that a proper selection of the most suitable drug is made. Sulphathiazole is most effective against staphylococcus with a urine of pH 7.5 ; in *Bact. coli* and *B. proteus* it acts best with the urine between pH 6.5 and 7.5 ; in *Str. faecalis* it is of value if the pH of the urine is kept about 5.5. The treatment may be combined with alkalies.

Ophthalmia neonatorum due to gonococcal infection may be treated with sulphadimidine or sulphathiazole in doses of 0.12 grm. (2 gr.) every three hours for the first twenty-four hours and then at less frequent intervals.

Administration of either sulphanilamide, sulphapyridine or sulphathiazole will cause rapid healing of **chancre** and also of **bubo.** In addition to the oral use the powder

may be dusted over the sore. The dose is 2 to 3 grms. daily in divided doses for five to ten days.

Sulphapyridine is a valuable drug in the treatment of **pneumococcus pneumonia.** It reduces the gross mortality in the proportion of three patients out of four and is effective in all types, particularly in types I, II, VII and VIII. Moreover, the incidence of empyema is lessened although clear effusion is common. To be effective the concentration in the blood must be 4 to 5 mg. per 100 mil. Sulphathiazole and sulphadiazine are also valuable drugs in this condition. The initial dose is 3 to 4 grms., *i.e.* 6 to 8 tablets, repeated in four hours. Subsequently 1 grm. is given every four hours until crisis or lysis occurs. A total of 20 to 25 grms. is usually considered sufficient. It is desirable that the treatment with 1 grm. doses every four hours should be continued for two to three days after the fall of temperature to prevent recurrence and maintain effective blood levels of 8 to 12 mg. per 100 mils.

In pneumococcal meningitis and peritonitis the use of sulphapyridine is also valuable, particularly if administered parenterally.

Sulphadiazine, sulphadimidine, and sulphamerazine possess chemotherapeutic activity of a high order and any of these will serve the therapeutic use. The choice of their selection will therefore depend on other factors, such as their relative toxicity. Sulphamerazine is better than sulphadiazine and sulphadimidine is still better and is least toxic.

For the treatment of **staphylococcal septicaemia** sulphathiazole is the drug of choice as it is especially toxic to *Staph. aureus* than any of the other related compounds. The treatment should be controlled by the determination of the concentration of the drug in the blood. For successful treatment, concentration of about 15 mg. p.c. is necessary, but this is not ordinarily possible with simple oral administration, therefore, it should be supplemented by the intravenous administration. For the treatment of carbuncles, cellulitis or acute osteomyelitis, the initial dose should be 4 grms. (60 grs.) followed by 1 grm. (15 grs.) every four hours and continued for one week or till the temperature becomes normal.

Sulphonamides have been used with good results both as preventive and in the treatment of **bubonic plague.** Plague bacillus is susceptible to the action of certain sulphonamides when present in adequate concentration. These will effect a cure in uncomplicated cases if a high loading dose is given, followed by further doses at four hourly intervals. Administration of sulphadiazine and sulphathiazole have successfully prevented plague among the contacts. Simeons and Chhatre obtained very good

results with sulphadiazine than with sulphathiazole. The mortality rate among cases treated within twenty-four hours was 6.61 p.c. whereas after twenty-four hours it rose to 19.7 p.c. Sokhey, Wagle and their associates as the result of 2000 cases in four epidemics came to the conclusion that sulphadiazine was better. Initial dose was 4 grm. and this was followed by 2 grm. after four hours, subsequently 1 grm. doses were given every four hours till the temperature and pulse rate remained normal for two days. Recent experience with streptomycin in the treatment of plague seems to establish that it is the drug of choice.

The outlook of **bacillary dysentery** has undergone considerable change with the introduction of sulphaguanidine and succinylsulphathiazole. Since these drugs are very little absorbed from the mucous membrane of the gut, they remain in the colon and exert their bacteriostatic influence therein. They have been used in acute bacillary dysentery, whether due to Shiga, Flexner or Sonne strains. They have also been used as a pre-operative and post-operative measure in surgery of the colon. These compounds may have a still wider field of usefulness in other intra-abdominal procedures. Sulphaguanidine has been used in **cholera** with good result.

Sulphathiazole and sulphapyridine have been used in the treatment of **gas-gangrene,** and they are active when due to *Cl. welchii*, less active against *Cl. septique*, and without any activity against *Cl. oedematiens*.

Sulphonamides have been used for their **local effect** in the form of powder or ointment for prevention of sepsis from wounds and burns. The wound should be thoroughly dusted with the powder and a single dose of 2 grm. given by the mouth. It may also be administered in the form of a thick suspension made by adding 2 grm. of powdered sulphanilamide to 100 mils of a 0.8 p.c. solution of sulphanilamide in normal saline. For treatment of burns an ointment formed by mixing sterile sulphanilamide powder with equal parts of sterile lanolin and cold cream is very satisfactory. It contains sulphanilamide 6 p.c. by weight. For the treatment of ulcers infected with streptococci a paste containing benzoic acid 0.2 p.c., sulphanilamide 0.8 p.c., glycerin 10 p.c. and powdered tragacanth 10 p.c. in Ringer's solution is used. A 5 p.c. solution of sulphathiazole sodium as a nasal spray is useful in sinusitis.

Although sulphonamides are useful as local application in different surgical conditions, their use in dermatological practice is attended with great risk, producing epidermal sensitisation of more or less permanent nature. It may be local sensitisation, general sensitisation, or photo-sensitivity. This may prevent their use at a future date for some serious conditions, such as pneumonia.

The following **general principles** for the use of sulpho-namides will be found useful :—

(1) They act better in acute infections than in chronic case and give better result when treatment is commenced early.

(2) On an average four-hourly administration is sufficient and since the drug is excreted quickly its use should be continued even at night if the concentration of the drug is to be maintained at the effective level.

(3) Parenteral administration is only indicated when a rapid action is required as in patients whose treatment has been neglected in patients who are unconscious or cannot swallow, and who are suffering from severe gastric irritation so that absorption of the drug is low. Since when administered parenterally the drug is rapidly excreted, the injections have to be repeated at frequent intervals to maintain adequate concentration of the drug in the blood.

(4) If no clinical response is observed, the treatment should not be prolonged beyond 5 to 7 days. If improvement is noticed the treatment may be prolonged for a further period of ten to fourteen days. If further administration is necessary it should be done after a rest of one or two days to help elimination of the drug.

(5) The action of sulphonamides is both quantitative and qualitative, therefore the higher the number of organisms the greater concentration of the drug is necessary. If the organisms are not killed quickly they often become drug resistant.

Causes of failure of sulphonamide therapy.—It should be fully realised that organisms sensitive to sulphonamides are exclusively bacteria. They are : Streptococcus haemolyticus (not non-haemolytic varieties), pneumococci, gonococci, staphylococci, meningococci, different varieties of dysentery bacilli, coliform and gas-gangrene organisms (not tetanus bacilli). Virus diseases are not susceptible to these compounds. Staphylococci are relatively resistant, and only the most powerful sulphonamides, like sulphathiazole, can affect them. Failure to respond may be due to variety of factors, viz.—(a) They are often given with insufficient clinical data ; (b) they are given in insufficient doses and for too short a period ; (c) other therapeutic measures are often neglected when these drugs are used ; (d) neglect to observe signs of toxicity or taking early precaution to prevent them ; (e) some obstruction to the transport of the drug to infected tissues due to very poor vascular supply or from other local conditions, or failure to reach the cerebrospinal fluid ; (f) development of some complications, e.g. onset of suppuration with inefficient drainage.

Combination Therapy.—Attempts are being made to administer two or more sulpha-drugs conjointly. It has been observed that such combination produces synergistic or additive effect, so that smaller doses of each compound can be given to produce the same effect than ordinarily required when either is given alone. This reduces or prevents toxic effect and chances of drug resistance. It has further been observed that a combination of equal amount of sulphadiazine, sulphathiazole and sulphamerazine reduces or eliminates chances of crystalluria even when no alkalies have been used. The results of combining one of the antibiotics with sulphonamides have also been striking. Thus it has been found that in pneumonia the mortality rate is considerably less when penicillin and sulphonamides are given together than when either of them used alone.

Modes of administration.—Sulphonamides may be administered by

(*a*) *Mouth,* this is the common route and will often be found sufficient.

(*b*) *Subcutaneous and intramuscular injection.*—For these routes neutral solutions should be used, *e.g.* soluseptasine or sodium

sulphacetamide (albucid is soluble); the sodium salts of sulphapyridine, sulphathiazole and sulphadiazine yield highly alkaline solution and should not be used. The intramuscular route should be avoided, as tissue necrosis, damage to the nerve resulting in wrist drop or foot drop have been recorded.

(c) *Intravenous injection* should be given only in case of extreme urgency and when the oral route is not possible.

(d) *Drip infusion*, intravenously or subcutaneously with saline, may be necessary in cases of staphylococcal septicaemia.

(e) *Rectal* administration is unsatisfactory. May be used for local lesions in the lower colon or rectum.

(f) *Local* application to wounds and other accessible regions, *e.g.* nose, pharynx, etc.

Different Compounds Compared

Sulphacetamide has properties similar to sulphanilamide. It was specially used in the treatment of **genito-urinary infections.** The sodium salt being feebly alkaline may be made neutral without forming a precipitate and is used in **ophthalmic practice** as a solution or ointment without any damage to the cornea. It is used in 10 to 30 p.c. solution and dropped into the eye every 2 hours in acute infections; in milder infections may be used every 4 hours. Valuable both as a prophylactic and curative in acute and **chronic conjunctivitis, blepharitis** and acute traumatic **corneal ulcers.**

Sulphanilamide.—It is absorbed within four to six hours though there is variation in different individuals. It is completely excreted within 48 to 72 hours both as free and conjugated acetylated inert form. Excretion is delayed in renal damage. Effect of a single dose lasts for six hours, therefore it should be administered every 4 to 6 hours. In man 3 grms. daily may produce toxic symptoms. Slight acidosis is common but is overcome by the use of alkalies. Sulphaemoglobinaemia and methaemoglobinaemia with cyanosis may occur. Cases of haemoglobinuria have been recorded.

Sulphathiazole, although slightly soluble, is quickly absorbed (80 p.c. in 3 to 6 hours) and equally quickly eliminated (60 to 90 p.c. in 24 hours) therefore toxic effects are less likely to occur, though haematuria is sometimes observed. 25 p.c. of the drug eliminated in the urine is in the acetylated form. Nausea, vomiting, mental depression and cyanosis are markedly less but drug fever and skin rashes are frequent. It is the most potent drug and is effective against a wide range of infections, viz., streptococcus, pneumococcus, gonococcus, meningococcus and staphylococcus. Next to penicillin it is the best drug for staphylococcal infection. Blood concentration varies. On an average 3 to 5 mg. per 100 mil. of blood being found with a dose of 4 to 6 grm. per day.

Sulphadiazine produces very little nausea, vomiting, drug fever, drug rash and other manifestations. It is absorbed and excreted more slowly than sulphanilamide and sulphathiazole and gives a higher concentration in the blood than other sulphonamides. In the treatment of pneumonia it may be used along the same lines and with the same precautions as sulphapyridine or sulphathiazole. Incidence of psychoses is greater than sulphathiazole. When 4-5 grm. is given orally, 60 p.c. is excreted with the urine in 24 hours, 75 p.c. in 72 hours, a quarter to a third in the conjugated form. 1 grm. every 6 hours (6 grm. daily) gives a concentration of 9.5 mg. When it is desired to increase excretion, sodium bicarbonate should be administered. To decrease the concentration in the urine glucose 5-10 p.c. should be given intravenously, or plenty of water given by the mouth.

Sulphamerazine is more quickly absorbed than sulphadiazine and more slowly excreted than sulphathiazole, so that the blood con-

centration is greater than with sulphadiazine. An average concentration of 8 mg. per 100 mil is attained in two hours, and 10 mg per 100 mil in four hours with a dose of 3.5 grm. per 150 pounds of body weight. Thus an adequate blood concentration may be maintained by a lower and less frequent dosage. It has been used in pneumonia, streptococcal and meningococcal infections, and the requisite concentration may be attained within four hours by the oral use of 3 to 4 grm. as an initial dose followed by 1 grm. dose every eight hours. For gonorrhoeal infection the plan is to use 1.5 grm. twice a day for 5 days. For meningitis a 5 p.c. solution of the sodium salt is first given intravenously (3 grm.) followed by oral administration in 1 grm. doses every 4 to 8 hours. As with all drugs of this group its use should be followed by liberal use of fluid. It is closely similar to sulphadiazine in toxicity and therapeutic activity, the chief advantage being the lower and less frequent dosage.

Sulphadimidine (Sulphamezathine) is more soluble than sulphadiazine. It is rapidly absorbed from the gastro-intestinal canal and slowly excreted so that a high blood concentration may be obtained by lesser dosage than can be obtained either with sulphanilamide or sulphapyridine. Its toxicity is less and therapeutic potency is similar to that of sulphadiazine.

Sulphapyridine.—It has some antipyretic action which may partly account for the rapid fall of temperature in pneumonia. It is highly toxic against pneumococcus, specially against types VII and VIII and exerts a definite action on the capsules of pneumococcus and does not give rise to sulphaemoglobinaemia and does not cause porphyrinuria in animal experiments in doses sixteen times the effective curative dose. It is less soluble than sulphanilamide and its absorption is irregular, therefore it becomes necessary to administer parenterally to maintain an adequate and constant blood level. It is also excreted slowly, 40 to 70 p.c. being excreted within 3 to 4 days. It is also acetylated to a higher degree, 60 to 70 p.c. of the drug in the urine appears in the acetylated form. Nausea and vomiting are common and may preclude its use. Haematuria may occur due to damage to the kidney tissue from sharp crystals of urinary calculi. It has been replaced by other drugs which cause less nausea and vomiting.

Sulphaguanidine is relatively less absorbed when given by the mouth than are other sulphonamides, therefore tends to remain in the colon and exerts its bacteriostatic influence there. Average blood concentration after a total of 6-12 grm. is 1.5 mg. per 100 mil. It should never be used as a substitute for sulphanilamide, sulphathiazole or sulphapyridine, nor to maintain drug levels in the blood. It should not be used in pneumonia, gonorrhoea, or in staphylococcic or streptococcic infections. Since only 1/3rd of the drug is absorbed it is less toxic than other sulphonamides, but should not be used longer than 14 days. It may give rise to haematuria, haemolytic anaemia, anuria or conjunctivitis. Valuable in all varieties of dysenteries, ulcerative colitis, cholera and as a prophylactic in abdominal operations.

Succinylsulphathiazole and **Sulphathalidine** are relatively non-toxic but may cause slight rise of temperature, anorexia, malaise and headache. Of the two, sulphathalidine is least toxic. They are very slightly absorbed after oral administration, only about 5 p.c. or less being excreted in the urine. Their activity is confined to the intestine. Effective dose of sulphasuxidine is 3 grm. (45 gr.) every four hours ; that of sulphathalidine 1½ grm. and should be preferred when diarrhoea is present. All these three compounds are useful in pre-operative preparation of both the small and large intestine, acute and chronic bacillary dysentery, diarrhoea, regional enteritis and chronic ulcerative colitis.

Proseptasine and Soluseptasine.—As compared with sulphanilamide, proseptasine is less toxic. Clinically it is useful in all conditions where sulphanilamide is used. For its alleged safety it can be used in cases of less severe haemolytic streptococcal infections. The same remark applies to soluseptasine.

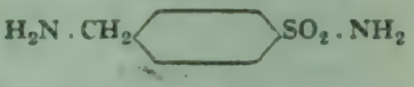
Uleron is not broken down to sulphanilamide and is effective against staphylococcal infections of mice and rabbits. It is the most widely used remedy in Germany for gonorrhoea but it is more toxic than sulphanilamide. It has often caused polyneuritis.

Sulphamidochrysoidin and Prontosil Soluble.—The former is not so popular now although it is largely used in the Continent. Prontosil soluble is useful when administration by the mouth is not possible and immediate result is necessary.

Gantrisin. (Not official).—It is 3, 4-dimethyl-5-sulphanilamido-isoxazole. It is more freely soluble than any other sulphonamides, 350 mg./100 mils at 6.0 *p*H. Acetylated compound at the same *p*H has a solubility of 110 mg./100 mils as compared to 80 or less for acetylated sulphadiazine and sulphamerazine. Specially recommended when a sulphonamide is required for a patient in whom renal complication has to be guarded against. Valuable in urinary tract infections, specially those due to *Pr. vulgaris.*

Dose.—For most infections, *initial dose*, 6 grm. followed by 1 grm. every 4 hours. For urinary infections, 2 grm. *initial dose* followed by 1 grm. every 4 hours.

Maphenide. (Not official). Syn.—*Marfanil.*—It is 4-amino-methylbenzene sulphonamide, and is chemically related to sulphanilamide with the difference that the amino group is not attached directly to the



benzene ring, but through a methyl group (*see* structural formula). Its antibacterial effect is not inhibited in the presence of pus or by *p*-aminobenzoic acid in common with other sulphonamides. It is suitable only for local application and is active against gas-gangrene organisms. It is used in old infected wounds and burns.

2. Antibiotics

It has been noticed that certain micro-organisms antagonise each other in the struggle for existence. Pasteur and Joubert as far back as 1877 observed that cultures of anthrax bacilli were inhibited by certain air bacilli. This natural antagonism has been termed "antibiosis". Later Waksman used the expression "Antibiotic" to therapeutic agents responsible for the phenomenon of antibiosis. The term antibiotic is now applied to chemical substances produced by micro-organisms, or their growth products, which possess an inhibitory effect on the growth and activity of other species of micro-organisms or destroy infective agents. Antibiotics are derived from metabolic products of fungi, mould, bacteria, actinomycetes, etc.

Penicillin, streptomycin, aureomycin, etc. are examples of antibiotics, *i.e.* they are naturally occurring antibacterial substances. With the knowledge of the chemistry of some of the antibiotics it has been possible to synthesise a few of them. Thus chloramphenicol, though produced by the

growth of *Streptomyces venezuelae*, may also be prepared synthetically. While it has been possible to prepare small amounts of penicillin synthetically, most of the commercial preparations are produced from natural sources.

PENICILLINUM
(Penicillin.)

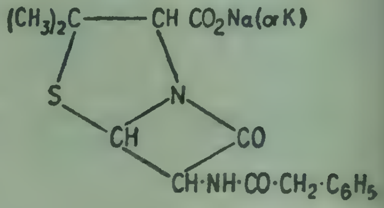
Source.—Penicillin is the sodium salt, calcium salt or potassium salt of the antimicrobial acid, which is produced when *Penicillium notatum* or related organisms are grown under appropriate conditions on or in a suitable culture medium. Non-specific impurities are removed as completely as possible, and the purified penicillin salt is dried under conditions designed to ensure the sterility and stability of the final product.

Penicillin occurs as (*a*) Penicillin (Sodium Salt), (*b*) Penicillin (Calcium Salt) or (*c*) Penicillin (Potassium Salt).

Characters.—Penicillin (Sodium Salt), Penicillin (Calcium Salt) or Penicillin (Potassium Salt), which have not been completely purified occur as pale yellow to light brown amorphous hygroscopic powders or larger particles or masses containing not less than 900 units per mg. When pure, Penicillin (Sodium Salt) is a white powder which may occur as crystals, granules or scales and Penicillin (Calcium Salt) is a white amorphous powder. Very *soluble* in water. Insoluble in fixed oils, and in liquid paraffin.

B. P. Dose.—To be determined by the physician.

Benzylpenicillinum. Syn.—Crystalline Penicillin G; Penicillin G.—Benzylpenicillin is either the crystalline sodium salt or the crystalline potassium salt of an antimicrobial acid which is produced by growing *Pencillium notatum*, or produced by any other means. Contains not less than 1550 Units per mg. (sodium salt) or 1480 Units per mg. (potassium salt).



Characters.—Occur as white finely crystalline powder. Very *soluble* in water : insoluble in fixed oils and in liquid paraffin.

B. P. Dose.—To be determined by the physician.

OFFICIAL PREPARATIONS

1. **Cremor Penicillini.** *Syn.—Penicillin Cream.*—Ordinarily 1000 Units per grm. should be dispensed.
2. **Cremor Penicillini Sterilisatus.** *Syn.—Sterilised Cream of Penicillin.*—Ordinarily 1000 Units per grm. shall be dispensed.
3. **Injectio Penicillini.—B. P. Dose.**—To be determined by the physician. Ordinarily Penicillin containing 200,000 Units per mil shall be dispensed.
4. **Injectio Penicillini Oleosa.—B. P. Dose.**—To be determined by the physician. Ordinarily 300,000 Units per mil shall be dispensed. N. B. The label should state (1) the name of the injection ; (2) the strength and the number of Units in a suitable dose-volume ; (3) "for intramuscular use only" ; (4) whether arachis oil or ethyl oleate has been used.
5. **Oculentum Penicillini.**—Penicillin (Calcium Salt) 1000 Units per grm.
6. **Trochisci Penicillini.**—Ordinarily 1000 Units shall be dispensed.
7. **Unguentum Penicillini.**—Ordinarily ointment containing 1000 Units per grm. shall be dispensed.

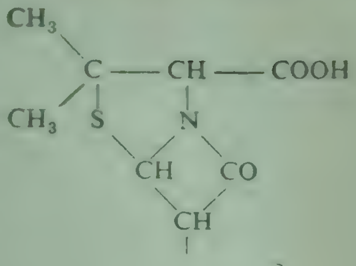
Procainae Benzylpenicillinum. Syn.—Procaine Penicillin G.—Procaine Benzylpenicillin is the monohydrate of the procaine salt of benzylpenicillin. Contains not less than 950 Units of penicillin per mg. and between 37.5 to 40.5 p.c. of procaine.

Characters.—A white crystalline powder ; slightly soluble in water (about 1 in 250).

Labelling.—Should mention total number of units in the container and the minimum number of units in mg.

B. P. Dose.—To be determined by the physician.

Chemistry.—Four chemical penicillins have been isolated in crystalline form. In fact pure crystalline penicillin is not a single compound but a mixture of four penicillins. In Great Britain they are numbered I, II, III and IV in accordance with their order of discovery; in America they are termed F, G, X and K. They are strong monobasic acids; dipeptides of a special type possessing a common nucleus but different side-chains. Only difference between them is the constitution of the radical R.



Penicillin I (F) R is $CH_2CH{=}CH.CH_2CH_3$ ($\triangle^4$-pentenyl)

Penicillin II (G) R is $CH_2.C_6H_5$ (benzyl)

Penicillin III (X) R is $CH_2.C_6H_4.OH$ (*p*-hydroxybenzyl)

Penicillin IV (K) R is $CH_2.(CH_2)_5.CH_3$ (*n*-heptyl)

Effects of different Penicillins.—All the varieties are active against penicillin sensitive-organisms but minor quantitative differences in their antibacterial power have been noticed. Most of the commercial preparations contain higher proportion of penicillin II (G). Penicillin III (X) is equally effective as penicillin II (G) against strains of *Staph. aureus* and *B. subtilis*; and 2 to 8 times more effective than penicillin II (G) against strains of streptococcus, pneumococcus, meningococcus and gonococcus *in vitro*. Penicillin IV (K) is no less active against sensitive micro-organisms than other penicillins but is rapidly destroyed in the living body.

Penicillin possesses the following physical and chemical properties, *viz.*—(1) It is an acid, unstable in acid form but stable as salt between *p*H 5 and *p*H 7: (2) that the salts of Ba, Ca, and Na are highly soluble and are brownish-yellow crystals; pure penicillin is colourless.

Historical.—In 1928 Fleming found that colonies of staphylococcus which were growing on a plate were affected by a colony of mould which developed on this growth. Fleming by subculture of the mould identified it as that of *Penicillium notatum*. When grown on nutrient broth, it was found to produce some substance which passed into the broth and possessed the property of stopping the growth of many bacteria. This active liquid was called *Penicillin*. Further experiments showed that while many of the bacteria responsible for producing diseases in man were affected, some disease producing organisms were insensitive to this liquid.

Sensitive and Resistant Bacteria.—Experiments so far made with partly purified extract showed that even when highly diluted penicillin will stop the growth of many organisms causing disease. It is effective against **gram-positive organisms**, both aerobic and anaerobic, although some are insensitive. Most **gram-negative organisms** are insensitive. The organisms may be classified as follows:—

Sensitive.—Staphylococcus aureus, Staphylococcus epidermis, Streptococcus (haemolytic), Streptococcus (viridans), Pneumococcus, Gonococcus, Meningococcus, M. catarrhalis, B. anthracis, C. diphtheria, Air borne micrococci, Sarcina, Actinomyces, Cl. welchii, Cl. septique, Cl. oedematiens, B. tetani, Spirochaetes, Morax-Axenfeld bacillus.

Insensitive.—Enterococcus, non-pathogenic gram-negative cocci found in the mouth, B. pyocyaneus, B. proteus, B. friedlander, B. coli, B. typhosus, B. dysenteriae, V. cholerae, Pasteurella, Brucella abortus and melitensis, M. tuberculosis, virus diseases.

Therefore only those diseases caused by sensitive bacteria are susceptible of cure by penicillin. The naturally resistant species of bacteria owe their resistance to their possession of *penicillinase*, the enzyme which destroys penicillin.

Inactivators.—Penicillin deteriorates at ordinary temperatures and is destroyed at 52°C. It should be kept at 4°C. The solution is more unstable and requires to be kept in a refrigerator. Thus it retains its potency for 3 hours at 37°, 24 hours at 25°, and for a week or more at 0° to 5°C. It is destroyed by acids, alkalies and by heat and inactivated by enzymes produced by some bacteria (penicillinase), oxidising agents, heavy metals, primary alcohols. Certain air bacteria also destroy it.

Pharmacology

Mechanism of action.—How penicillin produces its antibiotic action is not clear. Except staphylococci lysis of bacteria does not occur. It is possible that the body cells help destruction and that penicillin renders the organisms easy prey to phagocytosis. It is now generally considered that the action is bacteriostatic at lower concentrations and bactericidal at higher levels. Its action is purely antibacterial and not antitoxic and does not interfere with the natural defences of the body or with the process of tissue repair.

Bigger has shown that penicillin not only restrains the growth of bacteria, but actually kills them. According to Bigger penicillin kills only dividing cells and that a very small proportion of dormant non-dividing cells are liable to survive ; these according to him must be allowed to grow by interrupting treatment in order to permit their growth, thus make them vulnerable to penicillin.

Penicillin in small concentrations inhibits and ultimately stops the oxygen uptake of sensitive bacteria during their stages of multiplication, while no such effect is seen during the resting phase. Penicillin thus appears to interfere with the enzymatic processes essential for multiplication of bacteria. It has been suggested that penicillin acts by interfering with the transfer of hydrogen in the cell. For it has been observed that penicillin is inactivated by sulphydryl (-SH) compound suggesting that it interferes with the function of -SH group which plays an important part in cell metabolism. Penicillin according to this view promotes dehydrogenation of -SH groups to S-S and thus interfers with the metabolism of the organism. This effect also occurs only during the period of growth.

Though penicillin resembles sulphonamides in its specificity, its mode of action is different. Thus it is not antagonised by *p*-aminobenzoic acid, peptones or pus. Further, penicillin can prevent the growth of sulphonamide-

resistant organisms, and the sulphonamides can inhibit the growth of penicillin-fast strains. Whereas sulphonamides act principally by slowing down the rate of growth, penicillin can cause rapid death and lysis of susceptible organisms.

It does not affect leucocytes in any therapeutic concentration. Since it is inactivated by heavy metals or by oxidation, for local treatment, the wound should not be cleansed by any commonly used antiseptics.

Synergistic effect.—It has been observed that sulphonamides help in the bacteriostatic action of penicillin, and the presence of even two parts in a million of sulphathiazole definitely increases the apparent titre of penicillin. Concentrations of sulphapyridine too low to inhibit bacterial growth greatly increase the effect *in vitro* of penicillin against *Staph. aureus*. Bigger believed that simultaneous administration of sulphathiazole doubled the efficacy of penicillin, and would therefore be useful in preventing multiplication of an infecting organism during the periods when the content of penicillin in the blood falls to a low level in intermittent therapy. It has been suggested that the effect is additive and penicillin reduces the total number of bacterial cells to limits within which the sulphonamide becomes completely inhibitory. Penicillin is said to have a synergistic effect in combination with other chemotherapeutic agents, such as arsenic and bismuth.

Absorption.—Penicillin is absorbed from the mouth and it has been detected in the blood from gelatin lozenges of 10,000 units allowed to slowly dissolve when kept in the mouth. Though absorbed after oral administration, it is inactivated by the gastric juice. It is freely absorbed from the intestine. Theoretically when administered by the rectum it should be destroyed by penicillinase producing organisms present in the bacterial flora of the rectum. Some observers have, however, shown that suppositories containing 300,000 to 1,000,000 units gave appreciable levels in the blood. Though the results were not uniform effective concentration could be maintained for a considerable time. 1,000,000 units gave a maximum serum level of about 0.8 unit per millilitre. Attempt to treat patients with salol-coated capsules showed no clinical improvement. However, penicillin administered orally in combination with a suitable buffer salt, such as trisodium citrate, was found to be therapeutically effective ; the effective doses were comparable to the routine dose used in parenteral administration. Combination of penicillin with sodium citrate given by the mouth, half an hour before meals, produces

greater and more prolonged increase of penicillin blood levels than when ingested without a buffer salt.*

After *intravenous injection* there is maximum serum level immediately, of which about 75 p.c. disappears within 15 minutes and about 90 p. c. at the end of 30 minutes, remaining 10 p. c. disappears within the next three or four hours. After *intramuscular injection* the blood concentration rises rapidly reaching its maximum within 15 to 30 minutes and remains more or less stationary for the next half hour and then gradually falls off. After *subcutaneous injection* maximal serum level is reached after 60 minutes. A single intramuscular dose of 15,000 units produces a blood level of 0.5 unit per mil ; with 100,000 units the level is 2 to 3 units per mil. To maintain a level of 0.5 unit per mil by intramuscular drip, 240,000 units are required in 24 hours. It is found in smaller amounts in the bile, in the peripheral blood, saliva, pancreatic juice and cerebrospinal fluid.

Effective bacteriostatic concentration varies with the organism. Adequate blood concentration is 0.3 to 0.5 units per mil and this has to be maintained.

Absorption from the *cerebrospinal cavities* is slow. After *intrathecal administration* or when introduced into a joint it has been found in these cavities in effective concentration at the end of 24 hours and even longer.

Clearance.—Since about 80 p.c. is excreted by way of the tubules and about 20 p.c. by the glomeruli, effective concentration is soon lost. Its excretion is delayed in cases of renal insufficiency causing high concentration in the blood for a prolonged period. Attempts have been made to delay excretion so that a bacteriostatic concentration may be maintained in the circulation for a longer time with the same expenditure of penicillin. By restriction of fluid intake to 1500 mils (3 pts.) and salt intake to 3 grm., blood levels up to 8 times, than obtainable with penicillin alone, can be achieved. 5 p.c. dextrose used as a vehicle is a simple and harmless procedure for prolonging the action. Another method is to incorporate with penicillin peanut oil containing about 3 p.c. beeswax. This about doubled the time during which penicillin could be found in the blood stream. This is generally administered in doses

*Preparations for oral use :

Sod. penicillin	400,000 i.u.
Sod. cit.	1/2 oz.
Syrup	1 oz.
Aq. destil.	ad 8 oz.
1 oz. contains	50,000 Units

Sod. penicillin	400,000 i.u.
Alum. Hydrox. Gel	4 oz.
Aq. destil.	ad 8 oz.

Oral penicillin with a sulphonamide :

Cal. penicillin	50,000 i.u.
Sulphanilamide	15 grs.
Sod. bicarb.	15 grs.
Sod. citras	30 grs.

Mix and make one powder.

of 300,000 units every 24 hours either as a single dose or in two doses 12 hours apart.

Penicillin G forms a complex with procaine which is sparingly soluble in saline and in oil. It has therefore been used to prolong the action and to maintain efficient blood levels for a longer period. Excretion is also delayed when procaine penicillin G in oil is gelled with 2 p.c. aluminium monostearate. A single dose of this suspension of 300,000 units maintains adequate blood concentration for 4 days, while a dose of 2,000,000 units maintains blood concentration for one week.

Prolonged maintenance of effective penicillin concentration has also been achieved by the simultaneous administration of substances which are excreted by the tubules and thus interfere with tubular excretion of penicillin, *e.g.* *p*-aminohippuric acid (PAHA) and carinamide. Since the effective dose of PAHA is too high its use has been given up in favour of the latter.

Carinamide (formerly known as caronamide) is 4-carboxyphenyl-methane sulphanilide. It acts by blocking the specific enzyme transport system responsible for the passage of penicillin through the tubular cells. It is however not eliminated by the tubules, possibly it is taken up by the enzyme system in competition with penicillin. The dose is 3 grm. every three hours orally, and this gives plasma concentrations from two to seven times more. Whether its use is followed by any untoward effects has yet to be established before it can be used widely.

Blood-brain-barrier.—Penicillin passes the blood-brain-barrier only in insignificant amount. It has been observed that in patients not suffering from meningitis, administration of even 100,000 units either intramuscularly or by continuous intravenous infusion, does not produce an assayable level of penicillin in the cerebrospinal fluid. On the other hand significant amount can be detected in meningitis. It is possible that penicillin acts in low concentration in the cerebrospinal fluid, and that in some cases it will inhibit the development of an infecting organism if its sensitivity is high. In most cases of purulent meningitis however progress of the infection is prevented only by much higher concentration than can be obtained by parenteral administration, and here intrathecal administration gives better result.

Toxicity of penicillin is remarkably low. Locally it is not an irritant even when applied to such delicate surface as cornea. When used by continuous intravenous drip method, very little untoward reaction is observed except thrombophlebitis which occurs after 48 hours. Only reactions shown are due to pyrogens, or to a normal febrile reaction due possibly to too rapid injection. Some pain,

which is of a temporary nature, is observed after intramuscular injection. Sometimes allergic phenomena may be encountered either in the form of urticarial rash, erythematovesicular group of reactions and contact dermatitis. Sometimes reaction may follow oral, intramuscular or aerosol administration. There may be fever, prostration, headache, mild leucocytosis, arthralgia and tender subcutaneous nodes. *Herxheimer reaction* is not uncommon in the treatment of syphilis.

Administration.—For penicillin treatment to be successful it is necessary to bring it into contact with the infecting microbes in effective concentration throughout the treatment so that it can act on them and inhibit, kill or dissolve these microbes. Two methods are generally adopted, namely, *local treatment* and *systemic treatment.* The advantage of local treatment is that penicillin can come in direct contact with the invading organism, *e. g.* pastilles in infection of the mouth and throat ; in the treatment of empyema ; or when injected directly into the spinal canal in cerebro-spinal meningitis.

Where local treatment is not possible, or in generalised infection, systemic treatment is necessary and parenteral administration should be the method of choice. Two methods may be adopted, viz. *intermittent* and *continuous*, either *subcutaneously*, *intramuscularly*, or *intravenously.* In general, with the intermittent method, the highest peak is followed by a period during which little penicillin remains in the blood stream ; on the other hand with continuous administration, the level of penicillin in blood is more or less constant depending on the amount infused.

Generally intramuscular route is preferred, 10,000 to 100,000 units in 1 to 10 mils of isotonic saline solution is injected every three to six hours depending on the desired blood level.

In this higher concentration of penicillin is maintained for a longer period, the technique is simpler and the injections better tolerated. Benzylpenicillin in oil may be given at longer intervals, once every 24 hours.

Penicillin is also administered by other routes. It has been administered into the *pericardial sac* in purulent pericarditis. For children and infants it has been given by continuous *intramedullary administration* in infections of the long bones. In respiratory infections the popular method is by inhalation (*aerosol*), the patient breathing a mist produced by a special apparatus or through an inhaler. A dose of 20,000 to 40,000 units every two to four hours, provides a high level in the sputum with sometimes antibacterial amounts in the circulating blood.

Units.—The quantity of penicillin administered is measured in terms of Oxford Unit. It is the amount of penicillin activity which formed a zone of inhibition 24 mm. in diameter around a cylinder in an agar plate inoculated with *Staph. aureus.* 1 mg. contains 1,667 International Units. Thus 20,000 units is equal to 12 mg. pure penicillin.

The **mega unit** is equivalent to 1,000,000 units, it has been adopted to prevent errors which may occur from dropping the number of naughts and to avoid difficulties in reading.

The Standard Preparation is a quantity of the sodium salt of a pure preparation of penicillin II, or G. The Unit is contained in 0.00065 mg. of the Standard Preparation at present in use (1947).

Dosage.—It has been the practice to administer 100,000 to 120,000 units daily by intramuscular injection every three hours, generally about 15,000 units with each injection. It is generally believed that a blood level of about 0.1 unit per mil is required to con-

trol most infections but this level is achieved for only a short period. It is now realised that a higher dose than 15,000 units with each injection is necessary and that better and more consistent results are obtained only with the higher dosage, 50,000 units or even more, every three hours is not regarded a large dose, and this will yield more rapid control of infection, greater preservation of tissue and increased rate of healing. In all cases the object should be to bring the infection under control as quickly as possible.

Mode of preparing penicillin solution.—Penicillin is extremely soluble and may be dissolved in small amounts of sterile distilled water, pyrogen-free water, or in sterile isotonic saline solution. Generally the solution contains 5000 units per mil. The solution should be kept with aseptic precautions and in ice chest and made fresh every day as it begins to deteriorate in contact with moisture and the rate of deterioration increases with temperature.

THERAPEUTICS

In order that penicillin should produce its maximum therapeutic effect it is essential to follow certain fundamental principles. To be effective it is necessary that the invading organism must be sensitive to penicillin and that penicillin should be brought into direct contact with the infecting micro-organism in adequate concentration and for sufficient length of time. Therefore the route of administration, duration of treatment and the dosage to be used have to be carefully considered. While it is true that the requisite conditions may be achieved by local treatment in the form of lotion, ointment, drops, lozenges, etc., according to the site of infection it is always desirable to supplement local therapy with systemic administration. Although in the majority of cases penicillin will reach the infecting bacteria by parenteral administration, there are certain exceptions which should be kept in mind. Thus in pleurisy, penicillin should be directly introduced into the infected serous cavity ; similarly, in meningitis, intrathecal administration is essential. In acute infections, if treated early, a few massive doses (100,000 to 500,000 units) at intervals of a few hours, will always produce spectacular results. It has been observed that chronic cases in general are more resistant than acute infections. The former therefore require more intensive and prolonged treatment. It has also to be noted that penicillin cannot replace surgery, although used early and freely it can prevent formation of sloughs and abscesses. An abscess when formed should be drained, similarly dead tissue, sequestra, etc., require surgical interference.

Local treatment.—The object of local treatment is to get penicillin in contact with the bacteria directly and not through the blood stream. It can be used either (a) as *simple solution* for injection or other local application, *e.g.* for irrigating wounds (250 to 1000 units per mil). Similarly 200 to 2000 units per mil can be used for application to conjunctiva in corneal ulcers, ophthalmia neonatorum,

conjunctivitis or blepharitis with success. Since the efficacy of treatment with eye washes depends on the concentration and frequency of application, these should be used at least every hour, or even at shorter intervals. The oculentum may be used in purulent conjunctivitis after irrigating the eye. In severe infection, systemic therapy may be supplemented ; (b) as *a cream or an ointment* in superficial ulcers, burns, impetigo and the like ; (c) as *dusting powder* ;* (d) as *lozenges or pastilles* in infections in the mouth. Since most of the microbes which commonly cause infection in the mouth and throat are sensitive to penicillin, these lozenges when kept in the mouth and allowed to dissolve slowly have a beneficial effect ; and (e) as *inhalation* (aerosol therapy) through a nebulizer in various infectious diseases of the respiratory tract. This method is being increasingly used as it produces a high local concentration and because the drug can be absorbed into the blood-stream in adequate bacteriolytic concentration. The usual strength is 25,000 units per mil and nebulized every three or four hours.†

Local treatment is also useful in the following conditions, *viz.*—

Meningitis.—Although after parenteral injection penicillin is found in the spinal fluid, its concentration is not so high as it is in the blood. Therefore in the treatment of meningitis it is introduced into the spinal cavity in strength of 1,000 units per mil, when it remains in the spinal fluid in effective concentration for 24 hours or longer. This has the further advantage of saving the patient from getting three or four-hourly injections to maintain effective concentration and with less amount of penicillin. Higher concentrations in the cerebrospinal fluid can be maintained by daily intrathecal injections of 25,000 units in 2 mils of distilled water or normal saline. Best results are obtained when the intrathecal administration is supplemented by parenteral injection of 50,000 units four hourly.

Empyema.—Since penicillin injected into the pleural cavity is not rapidly absorbed, a few local injections of 30,000 to 50,000 units in 30 to 50 mils of saline solution together with aspiration of the pus will sterilise the empyema provided it is caused by penicillin sensitive organism. This procedure is carried out once every 24 to 48 hours. Systemic use of large doses (100,000 units six-hourly) reaches an empyema cavity in sufficient concentration to sterilise it, but local injection is more effective and economical.

Suppurative arthritis may be successfully treated by injection of penicillin into the joint. As much as 20,000 units in 10 mils of isotonic saline solution may be instilled into the joint after aspiration.

Bronchiectasis.—Penicillin has been used intramuscularly, by intratrachial or intrabronchial instillation, by inhalation or by combination of all these methods. Highest concentration in the sputum is obtained by intratrachial administration, by inhalation less, and by intramuscular injection least. Improvement is observed as long as treatment is continued but does not persist long after discontinuation of treatment. Since the treatment has no effect on cavitation reinfection soon occurs.

* Cal. penicillin	50,000-150,000 i.u.
Sulphathiazol. (finely powdered)	1 oz.

† Cal. penicillin	1 mega unit
Liq. adrenalin.	30 ms.
Aq. destil.	3 oz.

Systemic treatment.—Penicillin has been used with remarkable success in most of the infections with sensitive organisms, specially in the following:

(*a*) *Staphylococcic infections* with or without bacteriaemia.—It has been found even superior to sulphonamides in cellulitis, carbuncle, osteomyelitis, pneumonia, etc. In these conditions it is given in doses of 60,000 to 340,000 units in 24 hours, lasting for 3 to 12 days, depending on the severity of the case.

(*b*) *Pneumococcic infections*, specially in pneumonia, empyema, arthritis and in all sulphonamide resistant cases. These respond rapidly and the duration of treatment varies from 3 to 5 days or longer. Suitable dosage for pneumonia is 200,000 to 500,000 units 2 or 3 times daily, when recovery is expected in 2 to 3 days time.

(*c*) In *bacterial endocarditis* the results were disappointing at first but encouraging results follow with large doses (1 million units a day) continued for weeks. In fact success depends upon duration of treatment and dosage.

(*d*) *Diphtheria.*—Although *C. diphtheriae* is penicillin sensitive, reports regarding its usefulness are not unanimous. There is however a general measure of agreement that it has no effect on the rate of clearance of the membrane or the incidence of toxic complications but clears the organism from upper respiratory tract. Local treatment is ineffective. It is valuable in controlling secondary infections and useful during convalescence and in chronic carriers.

(*e*) *Gonococcic infections* including urethritis, salpingitis, arthritis. Its action in gonorrhoea is dramatic, generally 100,000 units split into five doses of 20,000 units at 3 hourly intervals cures almost every case. Concentration of solution being 5,000 units per mil. A single injection of 300,000 units will often cause complete eradication of the disease in most cases. As compared to sulphonamides its action is more rapid and uniformly successful. It is equally effective both in acute and chronic cases and is non-toxic.

(*f*) In *urinary infections* from *Bact. coli* sulphonamides are more helpful than penicillin, but it is extremely effective in *Staph. aureus* and *albus* infections of the kidney and in perinephric abscess, usual effective dose is 100 to 200 million units daily.

(*g*) *Gas-gangrene.* Here penicillin is useful as a supplement to standard methods of treatment, *e.g.* by surgical measures and use of anti-serum. 1000 units per mil should be applied directly to the wounds three times daily together with parenteral administration of 100,000 to 500,000 units twice daily intramuscularly.

(*h*) *Streptococcic viridans and haemolyticus.* Thes are extremely susceptible to penicillin and respond t 100,000 units daily given in 20,000 units at 4 hourly inter vals intramuscularly.

(*i*) *Syphilis.*—Penicillin is now recognised as the dru of choice in syphilis, although there exists some differenc of opinion as to adjuvant treatment. In the United States no additional treatment is recommended in any type o syphilis, while in the Continent and in England, penicilli treatment is supplemented by intramuscular injections o bismuth, though the length of treatment with bismuth i for three to six months in England and two to four year in France. In early syphilis, 600,000 units intramuscularl once daily for eight days followed by weekly injections o bismuth for ten weeks have been recommended as givin the best results. In case of relapse, penicillin injection i given daily for twelve days followed as usual by bismuth injection. After a rest period of four weeks, bismuth in- jections are given weekly for another period of ten weeks Good results have also been obtained by using procain penicillin G in oil gelled with 2 p.c. aluminium monostearate 1.2 million units are given once a week for two weeks, o alternatively, 600,000 units twice weekly for three weeks Fewer failures occur when the treatment is combined with a modified course of oxophenarsine. This consists o 2,400,000 units of penicillin in 7½ days and ten daily injec- tions of 1 gr. or 60 mg. of oxophenarsine. As a rule n toxic reactions are observed. If, however, they do occur, arsenic treatment should be stopped and penicillin con- tinued in dosage of *six to eight* mega units in 10 to 14 days. It has been observed that bismuth therapy combined with oxophenarsine and penicillin treatment reduces the relapse rate to a minimum. In congenital syphilis penicillin is superior to any other form of treatment in the early stages and the younger the child, the better is the response. In older child, penicillin treatment followed by arsenic gives better result. The chief advantage of penicillin over other forms of treatment is its freedom from toxicity, conve- nience of administration and the shorter course. In neurosyphilis penicillin is also the drug of choice.

Miscellaneous uses.—Penicillin is supposed to be the best remedy in **agranulocytosis** when used in doses of 20,000 to 40,000 units every three hours day and night for 4 to 10 days. It controls secondary infection and the bone marrow is given a chance to recover spontaneously. It also improves **macrocytic anaemia** and helps bone marrow to function normally possibly by interfering with bacterial metabolism thus releasing the haemopoietic factor, or by destroying the toxins produced by bacteria which have a deleterious effect on the bone marrow.

For the treatment of **anthrax** the initial intramuscular dose should be 500,000 units followed by 100,000 units every three or four hours. Most strains of **actinomycosis** are susceptible to penicillin when used in doses of 200,000 to 300,000 units daily for three weeks.

Prophylactic use of penicillin.—This has great possibilities, *e.g.* in the case of operation through infected tissues. Penicillin may be given for a day or two to reduce the amount of infection before operation is undertaken and continued for a few days until the leucocytic barrier is built up. It is usual to give 50,000 to 100,000 units immediately before the operation.

STREPTOMYCINI ET CALCII CHLORIDUM

(Streptomyc. et Calc. Chlorid.).

Streptomycin-Calcium Chloride is the calcium chloride double salt of an antimicrobial complex organic base or of a mixture of such bases produced by *Streptomyces griseus*, or a substance having chemical and biological properties identical with those of the foregoing substances, produced by other living organisms or by any other means.

Characters.—A white solid containing not less than 600 Units per mg.; hygroscopic. Very *soluble* in water; almost insoluble in alcohol (95 p.c.) in chloroform and in solvent ether.

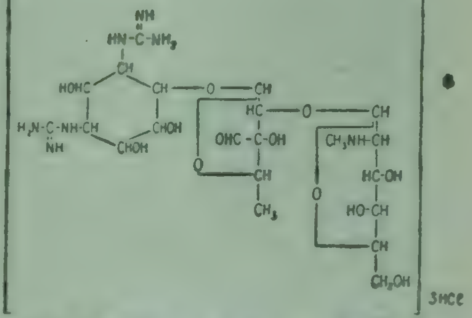
Labelling.—The label on the container states (1) the total number of Units in the container; (2) the minimum number of Units per mg.

B. P. Dose.—To be determined by the physician.

Official Preparation

1. **Injectio Streptomycini et Calcii Chloridi.**—A solution of Streptomycin-Calcium Chloride in water for injection. **B. P. Dose.**—To be determined by the physician. N. B. When no strength is stated, 250,000 Units per mil shall be dispensed for intramuscular injection.

STREPTOMYCINI HYDROCHLORIDUM.—Streptomycin Hydrochloride is the hydrochloride of an antimicrobial complex organic base or a mixture of such bases produced by *Streptomyces griseus*, or a substance having chemical and biological properties identical with those of foregoing substances, produced by other living organisms or by any other means.



$C_{21}H_{39}O_{12}N_7.3HCl$ . . . . Mol Wt. 691·0

Characters.—A white powder containing not less than 600 Units per mg. Very *soluble* in water; almost insoluble in alcohol (95 p.c.), in chloroform and in solvent ether.

B. P. Dose.—To be determined by the physician.

N. B. When Stremtomycin is prescribed, Streptomycin-Calcium chloride shall be supplied.

Official Preparation

1. **Injectio Streptomycini Hydrochloridi.**—**B. P. Dose.**—To be determined by the physician. N. B. When no strength is stated, 250,000 Units per mil shall be dispensed.

STREPTOMYCINI SULPHAS.—Streptomycin Sulphate is sulphate of an antimicrobial complex organic base or of a mix of such bases produced by *Streptomyces griseus*, or a subst having chemical and biological properties identical with those of foregoing substances, produced by other living organisms or by other means.

Characters.—A white solid containing not less than 600 U per mg. Very soluble in water; almost insoluble in alcohol (95 p in chloroform and in solvent ether.

Labelling.—Same as Streptomycin Calcium chloride.

B. P. Dose.—To be determined by the physician.

Official Preparation

1. **Injectio Streptomycini Sulphatis.**—B. P. Dose.—To be determined by physician. N. B. When no strength of injection is stated, [illegible] Units pe shall be supplied.

DIHYDROSTREPTOMYCINUM.—Dihydrostreptomycin may prepared by the hydrogenation of streptomycin. It occurs as Dihydrostreptomycin Hydrochloride or (*b*) Dihydrostreptomy Sulphate.

Characters.—A white solid containing not less than 600 Units per mg. soluble in water; almost insoluble in alcohol (95 p.c.), in chloroform and solvent ether.

Labelling.—(1) Whether the contents are Dihydrostreptomycin Hydrochlori Sulphate; (2) total number of Units in the container; (3) the minimum nu of Units per mg.

B. P. Dose.—To be determined by the physician.

Official Preparation

1. **Injectio Dihydrostreptomycini.**—B. P. Dose.—To be determined by physician. N. B. When no strength is stated, an injection containing [illegible] U per mil shall be dispensed.

Pharmacology

The results which followed the use of epoch maki discovery of penicillin, the first antibiotic, and the f that certain organisms were not affected by it, stimula search for other antibiotics which will produce effect organisms which were either penicillin-fast or are influenced by penicillin. Streptomycin is active agai those organisms which are not susceptible to penici and this property makes it a valuable therapeutic agen

Mechanism of action.—The exact mode of action streptomycin is not clear, although it acts as a **bacte static** for susceptible organisms in low concentrations **bactericide** at higher levels. Streptomycin on hydrol yields **streptidine** and **streptobiosamine.** The former diguanide compound related to inositol, and this combi with nucleic acid an essential metabolite for bacterial It has further been suggested that streptomycin combi with thiol group (-SH) also essential for bacterial me bolism.

Absorption and clearance.—Streptomycin is not sorbed by the gastro-intestinal tract nor it is destroyed the gut; but the susceptible organisms present in bowels can be reduced in number. It passes through intestine relatively unchanged. It is rapidly absor when administered subcutaneously or intramuscular

fter intramuscular injection blood-level reaches its peak one to two hours and then gradually falls. Intravenous ministration of 600,000 units produces a blood level of units per millilitre in fifteen minutes; after intramuscular injection in 30 minutes; and after subcutaneous jection after 60 minutes. Antibacterial concentration n be maintained by intramuscular injection every 12 urs. It passes into the gall-bladder and is concentrated the bile and has been found in the ascitic and pleural id in the same concentration as in the blood. In normal dividual its diffusion in the cerebrospinal fluid is very w, but the presence of an inflammation, as in meningitis, cilitates its diffusion. It is excreted less rapidly than enicillin. About one-half to three-quarters of the amount dministered intramuscularly is excreted in the urine uring the first 2 hours, only small amounts being passed ut with the stool.

Administration and dosage.—Average daily dose for n adult is 600,000 to 1,200,000 units and may be more. ince it is excreted slowly effective blood-levels could be btained by intramuscular injections at 12-hours intervals. The injections are given into the gluteus or deltoid muscle. grm. (600,000 units) is dissolved in 4 mils of normal aline or in water for injection, and administered in two njections daily. *Intravenous route* has no advantage over ntramuscular administration. *Oral* administration is used when it is desired to localise its effects in the gut. *Intrathecal route* is chosen when a high concentration is necessary in the cerebrospinal fluid, as in meningitis. As much as 15,000 to 60,000 units (25 to 100 mg.) in 5 or 10 mils of isotonic saline solution have been used without evidence of any serious reaction. This may be given every 24 to 48 hours. Before intrathecal injection is given sufficient spinal fluid may be withdrawn for determining streptomycin level and for bacteriological examination. For *local use* it is injected directly into the empyema or abscess cavities; 10,000 to 100,000 units per mil of normal saline are generally used.

Dihydrostreptomycin has properties similar to original streptomycin, but it is less toxic. With this vestibular damage is less common and it is well tolerated by those in whom streptomycin produces allergic symptoms. It is ineffective against tubercle bacilli which have become resistant to the parent compound. It however produces more severe local reaction. It can be used safely in larger doses and for prolonged periods. It is not advisable to use it intrathecally.

Limitations.—Apart from therapeutic limitations, it has two disadvantages, namely, (1) toxicity; and (2) tendency of the organisms to develop resistant strains.

Toxic reactions.—Minor toxic symptoms are flushing of the face, headache and fall of blood pressure. A very common symptom is vertigo. Symptoms resembling anaphylactic shock or histamine-like reaction have also been observed. These include nausea, vomiting, rise of temperature, maculo-papular rash or generalised urticaria. These are more common after intravenous injection. More serious toxic manifestation is the neurotoxic effect on the 8th nerve, either the vestibular or the auditory branch, or both, giving rise to tinnitus and deafness. These appear after eight weeks of treatment. Fortunately these disappear on stoppage of the drug. It may cause irritation of the kidneys as evidenced by albumin and casts in the urine. Eosinophilia of more than 6 p.c. may occur but this does not necessarily mean discontinuance of treatment.

Drug resistance.—In the treatment of pulmonary tuberculosis the bacilli become resistant, generally after six weeks or more but may be earlier and once they become resistant they usually remain so permanently and streptomycin will have no effect, nevertheless patients carrying resistant tubercle bacilli may infect others and the patients so infected will not yield to streptomycin. If however *p*-aminosalicylic acid is used in adequate doses concurrently with streptomycin there is distinct reduction in the incidence of streptomycin resistant tubercle bacilli.

THERAPEUTIC USES

Streptomycin is a valuable antibiotic and is an effective bacteriostatic and bacteriolytic agent against most gram-negative and acid-fast micro-organisms as also against a number of gram-positive penicillin-insensitive bacteria. It is a valuable therapeutic agent in gram-negative infections of the urinary tract, bacteriaemia, bacterial endocarditis, tularaemia, H. influenzae, and other gram-negative forms of meningitis, Shigella dysenteries and pneumonia due to Friedlander bacillus.

Penicillin is the drug of choice in most infections with staphylococcus, streptococcus, pneumococcus and meningococcus and streptomycin is only indicated if the strains are penicillin resistant.

In the treatment of **tuberculosis** the use of streptomycin seems more promising than any previous chemotherapeutic agent. In man prolonged administration is free from serious toxic reactions, possibly some of the reactions reported were due to impurities. Its use brings about temporary or prolonged remission of the symptoms and physical signs in most cases of tuberculous **meningitis** and **miliary tuberculosis.** For meningitis it may be administered both intrathecally and intramuscularly. In pulmonary tuberculosis it is generally administered in 1 grm. doses daily given in two injections, and unless any toxic symptoms are noticed may be continued for several weeks. 60 to 90 such injections may be given. Within a few weeks some of the severe symptoms may disappear, but X-ray improvement is slower, usually requires two to three months. Best results are obtained in exudative type. It is a valuable adjunct in the surgical treatment of vari-

ous forms of tuberculosis. Hinshaw et al. found that in the treatment of tuberculosis of the bone and joint, streptomycin was most effective when the infection was confined to the synovial membrane and that the peripheral joints responded more readily than those of the spine.

The following conclusions and recommendations of the Committee on Therapy of the American Trudeau Society and its Sub-Committee on Streptomycin Therapy will be of interest :—

(1) Intensive parenteral and intrathecal therapy is advised in **tuberculous meningitis.**

(2) Early treatment is advised in acute haematogenous **miliary tuberculosis.**

(3) In more severe cases of tuberculous laryngitis and ulcerating tuberculous lesions of the mucosa of the oropharynx.

(4) In progressive ulcerating tuberculous lesions of the **tracheobronchial tree.**

(5) In the treatment of recent but extensive and progressing pulmonary lesions, especially when these are diffuse and finely disseminated rather than appearing as large, dense, localized shadows **in X-ray photographs.**

(6) In acute ulcerative tuberculous enteritis.

(7) More extensive observations are necessary to assess its value in (a) prophylactic treatment before and after surgical procedures ; (b) tuberculosis of the genito-urinary tract and of bones and joints ; (c) tuberculosis of the skin, tuberculous lymphadenitis without sinus formation, and (d) ocular tuberculosis.

Streptomycin **is not recommended for**

1. Chronic fibroid or fibrocaseous pulmonary tuberculosis.
2. Acute destructive and apparently terminal types of pulmonary tuberculosis.
3. Minimal or early moderately advanced pulmonary tuberculosis with favourable prognosis.
4. In chronic empyema of tuberculous origin.

In **tularaemia** it gives good result when used in 1 to 2 grm. doses twice a day for 7 to 10 days.

Because of the slow elimination of streptomycin its administration in doses 0.3, 0.4 and 0.5 grm. in **gonorrhoea** cures almost all cases with a single injection. Successful results have been reported in the treatment of **subacute bacterial endocarditis** when the etiological agent is *Str. viridans faecalis* type which is highly resistant to penicillin. The dose used was 3 grm. daily divided into six doses for a period of 19 days. Its value in brucellosis, typhoid fever and Salmonella infections have not been established.

It has been used with success in **bubonic** and **septicaemic plague** and some consider it a specific in this disease. The minimum dose required is 1 to 2 grm. while the maximum is 8 grm. spread over four to five days, 0.5 grm. being administered every six hours.

Causes of failure of streptomycin :—

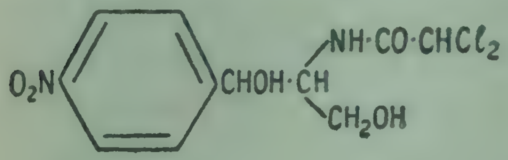
1. Treatment in cases with streptomycin resistant organisms.
2. Development of streptomycin resistant organisms.
3. Not used in sufficient doses to produce adequate blood levels.
4. Change in the bacterial flora during treatment.

CHLORAMPHENICOL

(Chloramphen.)

Syn.—Chloromycetin.

Source and Characters.—Chloramphenicol is D-(-)-threo-2-dichloroacetamido-1-p-nitrophenyl-1:3-propanediol, an antibiotic produced by the growth of *Streptomyces venezuelae*, or prepared synthetically. Fine white or greyish white or yellowish-white crystals, needles or elongated plates; taste bitter. Slightly *soluble* in water; freely in alcohol (95 p.c.).



B. P. Dose.—To be determined by the physician.

Pharmacology and Therapeutics

Chloramphenicol is absorbed from the gastro-intestinal tract and is readily eliminated or inactivated. It is active in high dilutions against a number of gram-positive and gram-negative organisms. About 10 p.c. is eliminated unchanged in the urine, the rest is excreted as inactive nitro compound. A dose of 2 grm. gives a concentration of 20 microgram per mil in the blood for eight hours. In patients suffering from typhus blood concentrations of about 5 microgram per mil can be maintained by the administration of 1 grm. daily in doses of 0.2 grm. at four hourly intervals.

It has been used by mouth in **typhoid** and **paratyphoid fevers** and has been found effective in controlling fever and toxaemia both in primary attack and in a relapse; initial dose recommended is 50 mg. per kg. of body-weight and subsequently 0.25 grm. every 2 hours until the temperature becomes normal which generally occurs in 36 to 72 hours. It has been observed that such initial loading doses are not necessary and often give rise to nausea, vomiting and vascular collapse due to liberation of endotoxin from the too rapidly killed bacilli. Three to four capsules of 0.25 grm. will be found to serve the purpose without the risk of producing any untoward symptoms. Sometimes relapse occurs when it has to be used again. The results are encouraging when used before tenth day. The duration of fever after commencement of treatment on an average is 3 to 5 days. But to avoid relapse the treatment should be continued for 7 days after the temperature comes down to normal in doses of one capsule every four hours. It is now advised that it can be given every 6 hours in divided doses with equally good results provided the daily dosage is 2 to 3 grm. Children under ten years should receive half to one-third of adult dose. It does not prevent the carrier state nor will cure established carriers.

It has also been found effective in destroying various

types of **rickettsia** and viruses of **psittacosis** group, and has given good result in **Rocky Mountain spotted fever.** Similar results follow its use in **scrub typhus.**

It has been found active against **plague** bacillus and may be used as a supplement to streptomycin treatment.

AUREOMYCIN

(Not official)

Syn.—Duomycin.

Aureomycin is derived from the soil organism *Streptomyces aureofaciens* which is so named because it produces a golden yellow colour in culture medium.

Characters.—In yellow crystals, soluble in acid and in alkaline solutions. A 2 per cent. solution of the hydrochloride in water has a pH of 4.5. The hydrochloride is highly stable in dry state and also in higher concentration in acid solution. In dilute solutions, it rapidly loses its activity unless kept in refrigerator at or below 20°C. It is rendered inert in the presence of broth, serum and whole blood.

PHARMACOLOGY

Antibiotic action.—Aureomycin is active against a number of gram-positive and gram-negative organisms and is particularly effective in infections with rickettsias and with viruses of the psittacosis-lymphogranuloma-venereum group and has a wider range than streptomycin. It is, however, less active than penicillin against most cocci and about as effective as streptomycin against most gram-negative bacilli. It is definitely inferior to streptomycin in tubercular infection.

Absorption, excretion and distribution.—Aureomycin is absorbed when given orally and appears in the urine within an hour and the maximum concentration is reached within 4 to 8 hours. The excretion continues, though in lower concentrations, for 3 to 4 days after the last dose.

When given orally a single dose of 1 grm. gives maximum serum concentration up to 4 mcgm. per mil in 3 to 6 hours. An effective blood level (2-4 up to 8 mcgm. per mil) can be maintained by giving the drug in doses of 1 grm. (10 mg/kg) every 4 to 6 hours. The drug diffuses into different body tissues and fluids including cerebro-spinal fluid in effective concentration particularly when inflamed. It passes through the placental barrier and reaches the foetal blood. It can also be demonstrated in bile, pleural and ascitic fluids.

Dosage and mode of administration.—*Oral.*—Moderately severe cases: *Initial dose,* 10 mg/kg. body-wt. (1/12 gr. per lb.) in 4 divided doses or 2 capsules of 250 mg. each every 6 hours or 1 capsule every 3 hours. *Maintenance dose,* 30 mg/kg. body-wt. (1/4 gr. per lb.) divided into 6 doses every 4 hours (total daily dose). Severe cases: *Initial dose,* 15 mg/kg. (1/8 gr. per lb.) and *total daily*

maintenance dose, 50-60 mg/kg. body-wt. (2/5 to 1/2 gr. per ℔.).

Intravenously.—In severe cases *initial* 5 mg/kg. (1/24 gr. per ℔.) body-wt. in one dose and *total daily mainenance dose,* 15 mg/kg. in 3 parts each, given every 8 hours.

Amounts up to 500 mg. (8 grs.) may be added to 500 to 1000 mils of 5 p.c. dextrose in water for intravenous injection, taking an hour or more, or up to 100 mg. (1½ gr.) in 10 mils of 0.75 p.c. sodium carbonate solution may be injected intravenously and repeated every 12 hours or oftener with replacement by oral therapy as soon as possible. The solution should be prepared immediately before use and injected slowly at the rate of 5 minutes for each 10 mils.

Solution of the hydrochloride is irritant when injected intramuscularly and is not recommended.

Toxicity.—Nausea, vomiting and diarrhoea are fairly common side effects after oral therapy. These are possibly due to the presence of some exogenous factors in the preparations available for oral administration. These side effects though common, rarely necessitate discontinuance of treatment and in majority of cases yield to ordinary symptomatic measures.

Mucous membrane changes particularly of the mouth and the tongue are common complication when used by the oral route. These are attributed to deficiency of Vitamin B-complex resulting from interference with normal synthesis by the intestinal bacteria, and simultaneous parenteral administration of Vitamin B-Complex also minimises this effect. When, however, aureomycin is administered intravenously, there is no such changes in mucous membrane.

Therapeutics

Locally.—A 0.5 p.c. solution of aureomycin borate controls ocular infections due to gram-positive cocci and gram-negative bacilli, in conjunction with oral use of the hydrochloride particularly in corneal ulcers and infections of deeper structures of the eye. 0.25 gm. (4 grs.) every four hours is useful in a variety of oral infections such as gingivitis, stomatitis, etc.

Aureomycin is of value in certain infections which are either not affected by other antibiotics or have become resistant to them. No cases have been recorded in which organisms develop fastness or resistance. In **rickettsial infections** like **Rocky Mountain spotted fever, typhus fever, scrub typhus and Q fever** the period of acute symptoms, fever, rash and the period of convalescence are greatly shortened irrespective of the time of commencement of treatment. In this respect, it is superior to *para*-aminobenzoic acid.

It is of definite value in some of the **viral infections** and is the drug of choice in **lymphogranuloma venereum** as well as in **psittacosis group.** Since it acts not only on the virus but also prevents secondary bacterial infection,

its use has been suggested as an adjunct to surgical and other measures in these conditions. It has been used in **brucellosis** and patients usually become symptomless within 72 hours and is the only drug which is beneficial in **primary atypical pneumonia.**

Urinary tract infections with organisms which have become resistant to sulphonamides or streptomycin are controlled effectively by aureomycin, but it is ineffective in *B. proteus* infections. For controlling staphylococcal infections, it is superior to penicillin. Cases of osteomyelitis improve where penicillin and streptomycin have failed.

Aureomycin is probably the first antibiotic of any value in the treatment of **amoebic infection** and is effective both against cystic as well as against vegetative forms of *E. histolytica.* 2 grm. by mouth given in 4 divided doses daily for one week reported to have produced relief of symptoms, healing of ulcers and disappearance of amoeba in majority of the cases. The relapse rate, however, which is definitely high when treated with aureomycin alone can be reduced to a minimum when it is combined with one or the other amoebicidal drugs. The beneficial effect of aureomycin is probably due to one or more of the following ways :—(1) a direct amoebicidal action in the intestinal wall ; (2) an indirect action on the amoeba through an alteration of the environmental bacterial flora.

TERRAMYCIN

(Not official)

Terramycin is an antibiotic derived from an actinomycete, *Streptomyces rimosus*, so named because of the cracked appearance of the growth on the surface of agar medium.

Chemistry.—Terramycin is a crystalline amphoteric substance of bright yellow colour forming stable crystalline salts with certain acids or bases. The hydrochloride when stored at room temperature will maintain its potency for about 12 months.

Absorption and clearance.—It is absorbed readily following either parenteral or oral administration and an adequate serum level (5 to 10 microgram) is maintained when 0.5 to 1.25 grm. is administered 6 hourly by mouth. It is excreted freely in urine, stool, bile, pleural fluid and placental blood but in a very small amount in cerebro-spinal fluid. A large proportion of the drug is excreted with the stool, and the high concentration in the faeces alters the bacterial flora of the intestinal tract.

Clinical indication.—Terramycin is effective against a wide variety of micro-organisms including many of the gram-positive and gram-negative bacteria both aerobic and anaerobic, spirochaetes, rickettsiae and certain of the

viruses. It may be used in all the conditions where penicillin, streptomycin or chloramphenicol have been found either ineffective or the organisms have developed resistance against any of these drugs. It has also been used with some success in the control of amoebiasis. Satisfactory results have yielded in pneumonia, acute follicular tonsillitis and septic sore throat. It is also being tried in cholera.

Dosage and administration.—2 to 3 grm. in capsules daily in divided doses of 0.25 grm. every 6 hours by mouth. In severe infections a high initial dose of 1 grm. (which maintains a blood level of approximately 25 mcgrm. per mil for 6 to 8 hours) or higher daily dosages (4 to 6 grm.) should be used. In children under 20 kg. body-weight, dosage of 100 to 150 mg. per kg. body-weight per day is advocated while in older children the adult dosages are indicated. Treatment should be continued for at least 48 hours after the temperature becomes normal and/or acute symptoms have subsided. The elixir is palatable and convenient in treating children.

Recently preparations for intravenous injection in severe cases have also been introduced.

Toxicity.—Terramycin is relatively non-toxic but an extensive clinical trial is still necessary before the drug can be declared non-toxic. Mild gastro-intestinal disturbances in the form of looseness of the bowel, nausea and vomiting have been noted in a small percentage of cases. Glossitis have also been observed. Mild reaction and those responding to the usual treatment of such conditions are not contra-indications to the further administration of terramycin. The drug should, however, be discontinued in severe and uncontrollable reactions.

Tyrothricin is another antibiotic isolated by Dubos from soil bacteria, *B. brevis,* and consists of two crystalline substances, *gramicidin* and *tyrocidin.* It is insoluble in water but soluble in alcohol and the solution is stable. Both gramicidin and tyrocidin possess bacteriostatic and bactericidal properties, the former against gram-positive, while the latter against some gram-negative species. When used either by the intravenous or intramuscular route, they cause haemolysis, therefore tyrothricin cannot be used for systemic infections. The use is confined to local application for the treatment of infected wounds and ulcers and other skin affections, and is less toxic than other commonly used germicides like the mercurials or tar compounds.

It may be used (*a*) as *aqueous solutions* prepared from an alcoholic concentrate ; 20 to 25 mg. per mil to be diluted with pyrogen free sterile distilled water before use ; (*b*) as *dry powder* (tyrothricin 500 mg. and boric acid 100 grm.), specially suitable as insufflation : (*c*) *as ointment* (0.3 mg. per grm. ointment of wool alcohols) for treatment of skin lesions, such as eczemoid dermatitis, impetigo, etc.

Class G : Drugs used in Tuberculosis

Para-aminosalicylic Acid, Thiacetazone, Gold, Streptomycin (q. v.)

PARA-AMINOSALICYLIC ACID

(Not official)

Syn.—P. A. S.; Paramisan.

Para-aminosalicylic Acid or 2-hydroxy-4-aminobenzoic acid is a white crystalline powder. It is used as sodium salt which is white when pure, but solutions prepared from commercially produced material are pale yellow in colour.

PHARMACOLOGY

Mechanism of action.—Bernheim in 1941 observed that benzoic acid and salicylic acid increased the oxygen uptake of tubercle bacilli suggesting that these or similar substances might be important metabolite of these organisms. Subsequently, Lehmann found that of all the substances which act by inhibiting the bacterial metabolite by a mechanism of biological competition, *p*-aminosalicylic acid (P.A.S.) was the most active *in vitro* for virulent human tubercle bacilli. Its action is not impaired by serum and resistant types do not appear to develop.

Besides its bacteriostatic effect, it possesses antitoxic and to some extent antipyretic properties.

Absorption, distribution and clearance.—P.A.S. or the sodium salt is rapidly absorbed when administered orally and quickly excreted. After a single dose maximum concentration in the blood is reached in about half to one hour and then gradually falls almost to zero in about 2 to 3 hours. After an oral dose of 14 grm. given in divided doses blood concentration is generally about 3 to 6 mg. per 100 mil. This, however, varies from 1 to 2 mg. or even up to 10 mg. per cent. depending upon the rate of absorption and excretion at different times and in different individuals. Because of its rapid destruction or excretion it is necessary to administer it several times a day to maintain efficient blood level.

After absorption, it is distributed in sufficient concentration in the different tissues, *e.g.* lungs, liver and kidney and also diffuses through cerebro-spinal fluid and pleural effusion.

It is almost entirely excreted in the urine either unchanged or as acetylated compound, the latter forming as much as 60 p.c. of the total amount taken. The major portion is excreted within 6 hours and the balance within 24 hours.

Toxicity.—P.A.S. is practically non-toxic. Occasionally nausea, vomiting or even diarrhoea may occur but these rarely require stoppage of treatment.

Therapeutics

Paramisan has been used in the treatment of tuberculosis of the lungs and most favourable results are obtained in acute exudative type of **pulmonary tuberculosis**. Improvement is noticed within a few days after treatment. The temperature falls first and as the treatment progresses, there is fall in pulse rate, appetite improves and the patient gains in weight and there is marked reduction of cough and sputum with lowering of sedimentation rate. Radiological signs of improvement, however, do not occur *pari passu* with clinical improvement.

The course of treatment varies according to the type of the case and response to treatment. A minimum of 3 to 6 months is generally necessary. A second course of a similar period may be given.

Its value in acute miliary tuberculosis and in meningitis has not been so favourable.

Administration and dosage.—The usual dose is 12 to 20 grm. daily in divided doses every 4 hours of 3 grm. each. The standard dose in U. S. A. is only 12 grm. daily. A daily total dose of 14 grm. administered every 4 hours in doses of 5, 3, 3 and 3 grm. will be found quite satisfactory. It should be given continuously but where a rest period is necessary one day in each week may be selected when its use should be withheld.

It is generally given dissolved in water and may be flavoured, if necessary, to cover the somewhat bitter taste. Cachets containing 1.5 grm. each may be taken to avoid unpleasant taste. 30 grm. of the sodium salt in 10 p.c. solution may be given daily by intravenous drip method without any harmful effect. Some develop thrombophlebitis.

Combined P. A. S. and streptomycin therapy.—It has been observed that when these two drugs are used together, they have an additive effect and is more effective than when either of them given alone. Moreover, this delays or prevents appearance of streptomycin resistant strain of tubercle bacillus in patients treated for prolonged periods. Although it has come to be regarded as an adjunct to treatment with streptomycin, it will remain the principal stand-by for streptomycin resistant cases.

THIACETAZONE

(Not official)

Syn.—Myvizone ; Conteben ; Myrizone ; Tibione.

Characters.—Thiacetazone is 4-acetyl-aminobenzaldehyde thiosemicarbazone. A pale yellow, finely crystalline powder, taste, bitter ; *almost* insoluble in water but more soluble in serum depending upon its pH ; sparingly soluble in common organic solvent.

ACTION AND USES

Of the several thiosemicarbazone derivatives introduced by Domagk and his collaborators, which possess chemotherapeutic effect against the tubercle bacillus, both *in vivo* and *in vitro*, the compound Thiacetazone, also called TB 1 698 is the most active. Given orally it is absorbed rapidly. The tuberculostatic property of the drug is ascribed to the acetyl radical but its actual mode of action is as yet unknown. Domagk believes that it exerts a direct action on the tubercle bacillus. It not only inhibits its growth but also produces morphological changes. Its activity is not inhibited by para-aminobenzoic acid and can be used locally as well as orally and parenterally. A dose of 200 mg. given orally produces blood concentration of 0.6-1 microgram per mil in three to five hours.

The most favourable response is observed in **pulmonary tuberculosis** specially in lesions associated with perifocal inflammatory processes. The more labile the lesions and better the blood supply, the greater is the effect. Chronic cases, however, react less favourably although cavernous processes often respond satisfactorily. The best tendency towards healing is observed in tuberculosis of the mucous membranes like tracheobronchial, laryngeal, intestinal and bladder tuberculosis. Miliary tuberculosis and tuberculous meningitis do not show any response. Further clinical trial is necessary in various forms and in various stages of tuberculosis before its value can be properly assessed. It cannot replace streptomycin or para-aminosalicylic acid but a judicious combination with these drugs will be found advantageous.

It is also being tried in the treatment of **leprosy**, but its use is still in the experimental stage. So far the reports are favourable.

Dosage.—The dosage varies from patient to patient depending upon the form and the state of the tuberculous process, response to the drug and finally the respective individual tolerance. But the usual average daily dose for adults is 2 mg/kg. body wt. (approx.) by mouth.

It is, however, desirable that the **initial dose** should be low, *i.e.* 12.5 to 25 mg. This may be slowly increased depending upon the subjective and objective condition of the patient. In general a dose of 200 to 300 mg. per day should not be exceeded. The treatment requires to be continued for four to six months.

Toxicity.—Thiacetazone is not free from toxic effects. At the beginning there may be gastro-intestinal troubles like anorexia, nausea and vomiting. But these usually disappear after some time even if the treatment is continued. Frequent toxic symptoms are a sensation of malaise, listlessness or sleepiness. Other toxic manifestations are skin rashes, conjunctivitis, moderate anaemia, agranulocytosis and some impairment of liver functions. If, however, the

dosage is properly regulated most of these manifestations are seldom noticed and/or easily controlled. Toxicity becomes greater with daily doses of 400 mg. or more.

SODII AUROTHIOMALAS

(Sod. Aurothiomal.)

Syn.—Myocrisin.

Sodium Aurothiomalate consists mainly of the sodium salt of aurothiomalic acid. Contains 44.5 to 46.0 p. c., of Au, and 10.8 to 11.3 p. c., of Na.

Characters.—A fine, pale yellow powder ; odour, slight. Hygroscopic. Very *soluble* in water.

B. P. Dose.—**By intramuscular injection :—1/6 gr. (10 mg.) increasing gradually to 1½ grs. (100 mg.) weekly.**

Official Preparation

1. **Injectio Sodii Aurothiomalatis.—B. P. Dose.**—By intramuscular injection : **1/6 gr. (10 mg.) increasing gradually to 1½ grs. (100 mg.), weekly.** N. B. When no dose is stated, a solution containing 1/6 gr. (10 mg.) in 15 ms. (1 mil) shall be supplied.

Auri et Sodii Thiosulphas. (*Not official*). **Syn.**—Sanocrysin; Crisalbin.

Characters.—A double thiosulphate of gold and sodium. Solid, snow-white substance in long needle-like crystals freely soluble in water. Solution, neutral.

Dose.—2/5 to 15 grs. or 25 mg. to 1 grm. in 10 mils of distilled water at intervals of 3 to 4 days, intravenously.

Calcium Aurothiomalate. (Not official).—Gold and Calcium Thiomalate is a pale yellow powder insoluble in water. Employed in the treatment of rheumatoid arthritis by intramuscular injection of a suspension in oil. It is less toxic than other gold compounds.

Action and Uses

Gold in different forms has been used empirically in diverse conditions. It is much less poisonous than other heavy metals, although its salts when given in toxic doses produce vomiting and purging. Given intravenously it acts like arsenic, and produces a fall of blood pressure by dilating the mesenteric vessels. In combination with arsenic it has been used in **tertiary syphilis,** and with bromides in epilepsy. It is used in **neurasthenia,** but any benefit that may follow its use is possibly mental.

Gold in the form of sanocrysin was introduced by Moellgaard in the treatment of tuberculosis. It has no marked effect on tubercle bacilli *in vitro*. How it acts is not clearly understood and it has no bactericidal effect on the *M. tuberculosis*. Probably it acts either by combining with the **sulphydryl elements** of tissue cells, or by stimulating phagocytosis. Because of the toxic effects, uncertain results and discovery of more potent remedies, it is now seldom used in the treatment of tuberculosis.

Sodium aurothiomalate is used in the treatment of **rheumatoid arthritis,** but its mode of action is not fully understood. British and Continental workers are agreed that beneficial results can be expected in about 70 p.c. of cases, and this improvement justifies its use despite the attendant risks. It should be considered as merely a unit

in the general scheme of treatment, *i.e.* removal of the aetiological factor and raising the patient's general resistance by every possible means.

Gold treatment has given favourable results in **lupus,** and its action has been explained as an indirect one, of the nature of a regressive influence on the pathological tissue and upon the altered blood vessels. In **lupus erythematosus** sanocrysin has been used with good results. The initial dose is 1 mg. (1/60 gr.) gradually increased to 50 mg. (3/4 gr.). It is given once a week intravenously.

Excretion.—About 50 p.c. of the metal is eliminated by the kidneys and partly by the intestine. Part is retained in the liver and muscle for a long time.

Like other heavy metals gold produces cumulative effects when given in large doses, or at frequent intervals.

Administration.—Myocrisin should be administered intramuscularly. The initial dose should be not more than 1/6 gr. (10 mg.) and given at an interval of 5 to 6 days, and the dose increased to 1/3 gr. (20 mg.) at the 2nd and 3/4 gr. (50 mg.) at the 3rd provided no untoward reactions occur. Subsequently 3/4 gr. (50 mg.) are given weekly till a total of 1 grm. has been given which will form a course. An interval of 12 weeks is given before starting another course. Generally two to three courses are required. The best results are obtained in the early cases, *i.e.* within two years of its onset.

The treatment should be stopped on the appearance of any of the following symptoms :—

(*a*) Generalised erythema of the skin ; continuation of treatment may lead to severe exfoliative dermatitis ; (*b*) albumen, casts and red blood cells in the urine. Appearance of albumen should be regarded as the danger signal. Urine should be examined before each injection is given ; (*c*) jaundice ; this is a sign of toxic hepatitis and should be regarded as a contraindication ; (*d*) purpura of the skin and mucous membranes is a sign of grave danger ; and indicates damage to the haemopoietic tissues ; and (*e*) leucopenia. Agranulocytosis, may result.

These symptoms are relieved by injections of calcium gluconate 10 mils of 10 p.c. solution, or sodium thiosulphate by the mouth or in severe cases intravenously. Use of Dimercaprol (BAL) increases excretion and gives prompt relief.

Solganol.—Di-sodium salt of 4-sulphomethlylamino-2-auromercaptobenzol-1-sulphonic acid. Contains 36.5 p.c. gold. In *tuberculosis*. *Dose.*—0.005 to 0.5 grm. (1/12 to 8 gr.). *Intravenously* to be given twice a week according to reaction. The dose to be cautiously increased.

Solganol-B is a solution, and **Solganol B Oleosum** is oily suspension of aurothioglucose, for *intramuscular and subcutaneous use.* The initial dose for Indian patients should not be more than one-fourth of the minimum dose recommended, and if this is not followed by any febrile reaction then the dose may be increased by the same amount with each subsequent injection. Unless the dose is carefully regulated it may cause severe reaction and make the condition worse. *Dose.*—5 mg. (1/12 gr.) gradually increased to 100 mg. (1½ gr.) intramuscularly.

Class H : Drugs used in Leprosy

Hydnocarpus Oil, Chaulmoogra Oil, Sulphones

OLEUM HYDNOCARPI

(Ol. Hydnocarp.)

Source.—Hydnocarpus Oil is a fatty oil obtained by cold expre sion from the fresh, ripe seeds of *Hydnocarpus Wightiana.*

Characters.—A yellowish, or brownish-yellow oil, or soft cream-coloured f with a characteristic odour and somewhat acrid taste. Partially *insoluble* in c alcohol (90 p.c.), freely *soluble* in hot alcohol (90 p.c.) ; miscible with solvent eth chloroform and carbon disulphide.

Composition.—Same as chaulmoogra oil.

B. P. Dose.—5 to 15 ms. increasing to **60 ms.** or **0.3 to 1 mil** increasing to **mils.**

Oleum Hydnocarpi Aethylicum. (Ol. Hydnocarp. Aeth.).—Eth Esters of Hydnocarpus Oil consists mainly of ethyl esters of chau moogric and hydnocarpic acids and is produced by esterifying th fatty acids of hydnocarpus oil with ethyl alcohol, or with industri methylated spirit.

Characters.—A colourless, or faintly yellow, limpid oil, with a characterist odour and slightly acrid taste. *Soluble* in not less than 6 volumes of alcohol (90 p.c. miscible with solvent ether, chloroform, and carbon disulphide.

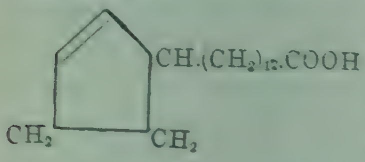
B. P. Dose.—5 to 15 ms. increasing to **60 ms.** or **0.3 to 1 mil** increasing to **mils.**

Official Preparations

1. **Injectio Olei Hydnocarpi.—B. P. Dose.**—By subcutaneous or intramuscula injection :—**30 ms.** (**2 mils**) increasing gradually to **75 ms.** (**5 mils**). By subcuta neous or intramuscular injection.
2. **Injectio Olei Hydnocarpi Aethylici.—B. P. Dose.—30 ms.** (**2 mils**) increas ing gradually to **75 ms.** (**5 mils**). By subcutaneous or intramuscular injection.

Oleum Chaulmoograe, I.P.L. (Ol. Chaulmoog.). **Syn.**—Gyno cardia Oil. ***Chaulmoogra tel,*** **Beng. Hind.**

Chaulmoogra Oil is the fatty oil obtained by cold expressio from the fresh ripe seeds of *Hydnocarpus kurzii* or other species o ***Hydnocarpus.***



Characters.—Yellow or brownish-yellow oil Below 25°C., a whitish, soft solid ; odour, charac teristic, **resembling that of rancid butter ; taste somewhat acrid. Sparingly *soluble* in** alcoho **(90 p.c.), soluble in benzene, in chloroform an** in solvent ether.

Composition.—(1) Glycerides of *Chaulmoog ric acid,* $C_{18}H_{32}O_2$. (2) Glycerides of *palmiti* ***acid* and fatty acids. (3) *Hydnocarpic acid.***

Non-official Preparation

1. **Sodii Hydnocarpas, B.P.C.** *Syn.—Alepol.*—Sodium salt of a fraction of the fatty acids of hydnocarpus oil. A fawn-coloured powder, odour, slight, resemblin hydnocarpus oil. A 3 p.c. solution is given intramuscularly, subcutaneously o **intravenously.** ***Dose.*—1 to 3 gr. or 60 to 200 mg.**

Pharmacology

Externally.—Chaulmoogra oil when rubbed into the skin stimulates the local circulation and the local nerves. If rubbed too long or every day for some time, it is a **rubefacient.**

Internally.—Hydnocarpus or chaulmoogra oil or their ethyl esters are efficient remedies for **leprosy.** How they act is not clearly understood. It is believed to act by producing a reaction with fever whereby the lepra cells rupture and liberate the bacilli which act as antigens and increase the immunity response. The other school main-

ms that they increase the blood lipase which dissolves he waxy or fatty coat of the bacilli thus making them avourable for the oils to act on. It is said that in this gion the large mononuclear leucocytes, which increase fter an injection, assist in the transport of the oil throughut the body. While others (Walker and Sweeney) maintain that these oils, because of the presence of unsaturated atty acids, possess a special bactericidal effect on acid fast acilli which is the underlying cause of the specificity of hese oils.

Read* found that in toxic doses the hydnocarpates roduce haemolysis of the red blood-corpuscles, renal irritation with haemoglobinuria, anorexia, nausea and vomitg. These effects are not observed in therapeutic doses. ther effects following their use are :—

Immediate effects.—Dizziness, choking sensation and pain in the est. Sometimes dimness or temporary loss of vision. The cause these reactions is not known.

Local effects.—Induration, pain and abscess formation, more mmon after subcutaneous injections than after intramuscular inctions. Regional lymph glands sometimes become enlarged or even cerated.

General symptoms.—Headache, malaise, fever, insomnia, anoxia, abdominal pain and a sensation of general heat. Albumin d casts, or even nephritis may appear. The so-called leprous retion consists of fever, cutaneous eruption, neuritis, arthritis and lammatory reactions of the eye (iritis or iridocyclitis).

THERAPEUTICS

Formerly these oils were used by the mouth, but pronged use in large doses upsets the stomach and therefore e ethyl esters of hydnocarpic and chaulmoogric acids are w used either intramuscularly or intravenously. The dium salts and esters of these acids being less irritating e generally used. Muir recommends the following E. C. O. mixture as effective, convenient and painless when ven intramuscularly. It consists of ethyl esters of fatty ids of hydnocarpus oil 1 mil, creosote (double distilled) mil, camphor 1 grm. and olive oil 2.5 mils. Of this 0.25 l is given twice a week, and gradually worked up to 2 5 mils by increases of 0.25 mil with each injection as g as no marked febrile or local reaction occurs. With s treatment the nodules become soft, disintegrated and entually are absorbed, while in early cases all clinical ns disappear after treatment extending over six months.

Prescribing hints.—The oral method is not so popular now. The [illegible] into the diseased patches should be the [illegible]. The area of the diseased skin is chosen and the [illegible] into the subcutaneous tissue and a fraction of the [illegible] injected, withdraw the needle partially and reinsert it at [illegible] and inject a little more, and in this way with one [illegible] the drug is injected at different angles. Al-

* Journal of Pharmacology and Experimental Therapeutics, XXIV, 1924.

ways inject into the loose subcutaneous tissue and not into the ski as this may cause sloughing. When large doses are required, intra muscular injections are given into the upper half of the glutea region, care being taken to avoid the region of the sciatic nerve Before pushing the piston home be sure that the needle has not en tered a vein.

SULFONES
(Not official)

These are derivatives of Diamino-diphenyl sulphone. Thes compounds have been tried in tuberculosis and leprosy. They wer not found to be of much value in tuberculosis but gave encouragin results in leprosy. Except Promin, which was too toxic when give orally, they are well tolerated when administered by the mouth The most common toxic effect is slow erythrocyte destruction. Infre quently, leucopenia and allergic dermatitis may occur. Haema turia and crystalluria have been observed with diasone when used i large doses at the beginning. Toxic effects like nausea, vomiting jaundice and confusional mental state may appear if the dosag schedule is not strictly adhered to. Urine examination, red an white cell counts and haemoglobin estimation should be done ever three weeks.

Promin. Syn.—*Promanide.*—It is sodium salt of *p-p'*-diaminodi phenyl-sulphone-N-N'-didextrose Sulphonate. It enters the cere brospinal fluid only in low concentration, and is excreted in the urine but being soluble it does not cause urinary blockage. On the basis that it inhibits production of tuberculosis in experimental animal it was used in human tuberculosis but it was found that huma being could not tolerate the drug as guinea-pigs. The report though encouraging were not convincing. A 40 p.c. solution use as 'misto' has been found beneficial in endobronchial ulcerations In the form of ointment or jelly (5 p.c.) it is used in tubercula abscesses and sinuses. In tuberculosis the daily dose is 1.6 grm. u to 3.2 grm. and may be continued for six months. The averag blood concentration on this dose is 2.4 mg. per 100 mil. Toxi symptoms are diminution of haemoglobin and erythrocytes ; cyano sis and gastro-intestinal disturbances ; agranulocytosis has als been noticed.

Promin has been used in **leprosy** intravenously. Commenc ing with 1 grm. doses daily and slowly increasing the dose by 1 grm every week to a maximum of 5 grm. It is generally given 6 day in the week for 2 weeks and then rest for one week ; after which another course of 2 weeks. This routine is to be continued for si months to 3 to 4 years. It is too toxic when given orally to allow effective therapeutic dosage, but intravenously it is effective an mildly toxic.

Promizole.—4, 2'-diaminophenyl-5'-thiozolyl-sulphone. It is les toxic than promin and is closely related to diasone. It has how ever not come up to the expectation in the treatment of tuberculo sis even though it has been used in doses of 12 to 16 grm. daily. I has given better results in leprosy than both promin and diasone It produces clinical improvement after six months' treatment Commencing with 0.5 grm. three times a day and increasing to a daily dosage of 6 grm.

Diasone.—It is disodium formaldehyde sulfoxylate diaminodi phenylsulphone. Diasone like other sulphones proved to be effect ive in arresting tuberculosis in the guinea-pig. It is less toxi than promin. But in human tuberculosis the treatment was followe by certain toxic symptoms, namely anorexia, flatulence, headache insomnia, nervousness and malaise with reduction of both haemo globin and red blood cells and appearance of cyanosis. It has bee

used in leprosy and Muir records result of treatment of 12 cases in England. The usual dose was 1 grm. daily. Commencing with 0.3 grm. given on alternate days three times weekly, increased, if no contra-indication was observed, by one capsule each day until a maximum of six capsules were given on each of three days a week. After three week's of full dosage a week's rest is given. When tolerance is developed the dosage is pushed up to 12 grm. a week for three weeks in each month.

Dosage as recommended by Cochrane is 0.3 grm. (5 gr.) once a day for one week, twice a day for one week and then thrice a day.

Sulphetrone.—It is also a derivative of diaminodiphenylsulphone and has been found to possess a high degree of activity against acid-fast organisms, chiefly *Mycobacterium tuberculosis* and *M. leprae.* Promising results have been found by its early use in lepromatous leprosy. In the neural type, sufficient data are not yet available to assess its value. It may be administered both orally and by injection. Parenteral route is now considered to be the route of choice. It is made up in a 50 p.c. solution in distilled water and then sterilised either by boiling or autoclaving. The following course of treatment is recommended : First week, 1 mil twice a week, and increase by 1 mil weekly until 3 mil twice a week is reached. If much pain is experienced make the solution 20 p.c. instead of 50 p.c. Its use in leprosy can be continued for a prolonged period. Its value in tuberculosis has not been established, although it is claimed to be of some value in the infiltrative type.

For oral use ; 1st week, 1 grm. per day ; 2nd week 2 grm. per day ; then 3 grm. daily.

According to Cochrane in Indian patients with hypopigmented macules of neural leprosy (maculo-anaesthetic lesions) these drugs are not of much value. In neural leprosy with deformity or threatened deformity, sulphone therapy may be harmful in that the acute nerve pain may increase the nerve damage and thus intensify the deformity. In these cases orthopaedic and physiotherapeutic measures will be more beneficial than sulphone therapy.*

GROUP XVIII

NUTRIENTS

Vitamins, Yeast, Cod-liver Oil, Halibut-liver Oil, Sucrose, Lactose, Dextrose, Glucose, Laevulose, Gelatin, Protein Hydrolysate, Ovolecithin.

VITAMINS

Observations made by Funk and others show that in addition to the different proximate principles of food there are certain accessory materials that are necessary either because they play an important role in the synthesis of the body, or influence in some indirect way the normal direction and character of the metabolism. These accessory substances are essential to normal growth and development. Ordinarily a well-balanced diet should supply an adequate amount of all the different vitamins. Vitamins resemble hormones in many respect and are often called "exogenous hormones". They are widely distributed in nature, and some like vitamin K, may be synthesised by the bacteria in the lower part of the intestinal tract. Similarly, vitamin D is also formed from ergosterol by

* *The Practitioner, April,* 1951.

exposure of the skin to sunlight. The part vitamins pla in the metabolism is not precisely clear in all in tances but some of them are now known to play a role i the oxidation-reduction processes in the body. Thus ribo flavine in the cell appears to be associated with protein an phosphoric acid, and to act as an oxidising enzyme. Th amide of nicotinic acid was identified as part of the tw enzymes concerned in oxidation-reduction reactions even before its identification as a vitamin. The vitamin B with pyrophosphoric acid acts as the co-enzyme of carb-oxylase, an enzyme essential for the breakdown of pyruvic acid in the body. Ascorbic acid has powerful reducing properties and is readily oxidised by free oxygen in the presence of a suitable enzyme ; the oxidation product, dehydro-ascorbic acid acts readily as a hydrogen acceptor. In this way it plays a role in the oxidation-reduction processes in the cell.

Vitamins exist in the foods in very minute quantities, and a vitamin free diet gives rise to certain diseases, generally known as deficiency diseases, and may even cause death. Rickets, pellagra, scurvy, beri-beri, xerophthalmia or keratomalacia, osteomalacia are some of the diseases caused by the lack of vitamins in the food. Green vegetables and fruits are rich in vitamins, and both man and animals obtain their vitamins from these sources. Vitamins are produced only in plants from which they pass directly with vegetable foods, and indirectly with animal foods, into the human system.

ANTIVITAMINS

Antivitamins are substances which antagonise the action of vitamins. But the term is usually applied to substances which counteract the action of vitamins by biological competition from similarities of their chemical constitution. Toxamins also antagonise the action of vitamins and are classed as antivitamins, although they act by some mechanism other than biological competition, probably by some toxic action.

Certain chemical analogues of vitamins, because of their structural resemblance, are antagonistic to some vitamins, competing with them for a position in some vital metabolic process (substrate competition). A typical example is antagonism between sulphonamides and PABA (a member of vitamin B-complex also an essential metabolite of some bacteria).

Other examples of antivitaminic action are inactivation of folic acid by 4-amino-folic acid ; biotin by avidin ; vitamin K by dicoumarol ; vitamin A and E by rancid fats and vitamin B_1 by carbohydrate.

Another antivitaminic substance of special interest is

phytic acid present in cereals (oatmeal and wheat flour) which antagonises the action of vitamin D and is rachitogenic. This anti-calcifying effect of phytic acid is not due to any toxic substance. Phytic acid combines with calcium and magnesium in the intestine forming a complex non-absorbable compound phytin which renders the calcium unavailable to the bones. This rachitogenic or anticalcifying effect can be neutralised by administration of vitamin D. The action of vitamin C is antagonised by *glucoascorbic acid* which when administered to guinae-pigs produces a scurvy-like condition.

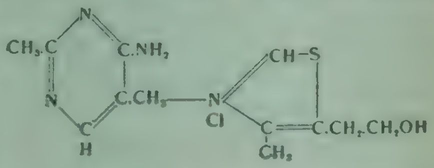
1. Water Soluble Vitamins

VITAMIN B COMPLEX

Vitamin B complex is water soluble and contains a large variety of different substances, all of which are present in yeast extract, rice polishings and liver. The important ones are vitamin B_1 or thiamine or aneurine ; and vitamin B_2 complex, which includes riboflavin or lactoflavin, nicotinic acid or amide of nicotinic acid ; pyridoxine and pantothenic acid, B_{12}, biotin, choline, *p*-aminobenzoic acid, inositol and folic acid

ANEURINAE HYDROCHLORIDUM. (Aneurin. Hydrochlor.) Syn.—Aneurine Chloride Hydrochloride ; Vitamin B_1 ; Thiamine Hydrochloride.

Aneurine Hydrochloride is 3-(4′-amino-2′-methylpyrimidyl-5′-methyl)-4-methyl-5-ß-hydroxyethylthiazolium chloride hydrochloride.



It may be obtained from rice polishings, yeast and other natural sources, or by synthesis. It contains from 20.4 to 21.2 p.c. of total Cl, and from 10.3 to 10.8 p.c. of Cl present as hydrochloride, and from 95 to 103 p.c. of anhydrous aneurine hydrochloride, all calculated with reference to the substance dried at 105°C.

Characters.—Colourless, monoclinic plates, usually in rosette-like clusters ; odour, characteristic ; taste, bitter. Readily *soluble* in water ; soluble in methyl alcohol ; almost insoluble in dehydrated alcohol, in solvent ether, and in acetone.

B. P. Dose. Prophylactic :—**1/30 to 1/12 gr.** or **2 to 5 mg.** (daily). Therapeutic :—**1/3 to 3/4 gr.** or **20 to 50 mg.** (daily).

Official Preparations

1. **Injectio Aneurinae Hydrochloridi.** *Syn.—Injection of Vitamin B_1 ; Thiamine Hydrochloride Injection.* B. P. Dose. **1/3 to 3/4 gr.** or **20 to 50 mg.** N. B. When no strength is stated, 2/5 gr. in 15 ms. shall be supplied.

2. **Tabellae Aneurinae Hydrochloridi.** *Syn.—Tablets of Vitamin B_1 ; Thiamine Hydrochloride Tablets.* B. P. Dose. Prophylactic (daily) :—**1/30 to 1/12 gr.** or **2 to 5 mg.** Therapeutic (daily) :—**1/3 to 3/4 gr.** or **20 to 50 mg.** N. B. When the quantity in each tablet is not mentioned, tablets containing **1/20 gr.** shall be supplied.

Perpolitiones Orizae, I. P. L. Syn.—Rice Bran.—Rice Polishings consist of the fine, flaky pericarp and seedcoat fragments, the embryo, aleurone layer, and outer adhering cells of the starchy endosperm of the grain (not parboiled) of *Oriza sativa*, and suitably defatted.

Each grm. contains the equivalent of not less than 15 micr grams of aneurine hydrochloride and 200 micrograms of nicoti acid.

PREPARATION

1. **Extractum Perpolitionum Orizae, I. P. L.** *Syn.—Extract of Rice Bran.*—C tains not less than 60 micrograms of vitamin B_1 in each mil. *Dose.*—1/2 to 1 or 15 to 30 mils. Each mil is equal to 14.5 grms. of rice polishing.

Vitamin B_1 has been isolated and synthesised as white crystalline powder. It is amino-peptide hydr chloride containing Cl, N and S. Its physiological activit is identical with the natural product. It withstands boi ing in acid medium, is more stable than ascorbic acid, bu less so than other vitamins. In neutral solution, a litt less than half is destroyed in four hours at 100°C., and i much less stable in alkalies.

It is absorbed from the gastro-intestinal tract and i stable in the gastric juice, but presence of bile causes los of thiamine. Its absorption is interfered with in persisten vomiting, pyloric stenosis and any condition where th usual dietary intake becomes very deficient as in chroni diarrhoea. It is not stored in the body in any appreciabl extent and any excess is excreted or destroyed.

Aneurine is associated with carbohydrate metabolism and in combination with pyrophosphoric acid it acts as co-enzyme of carboxylase, an enzyme essential for th breakdown of pyruvic acid, one of the degradation product in the catalytic breakdown of glucose in the body. It absence prevents the oxidation of pyruvic acid so tha there is an accumulation of lactic acid and pyruvic acid an the nerve cells fail to function properly. The nervou system and the heart are the organs most markedly an early affected.

Partial deficiency of vitamin B_1 if continued lon causes intestinal stasis, wasting of the bowels, retentio of the putrid food residue and absorption of the product of putrefaction, and auto-intoxication. Average daily re quirement for an adult is 1 mg. ; 0.03 mg. being require for each 100 calories. During pregnancy and lactatio the need is five times more. Deficiency of this vitami causes beri-beri and analogous disease in animals. Thi is characterised by anorexia, loss of flesh and strengt polyneuritis, oedema and dilatation of the heart, commonl known as beri-beri heart. Minor degree of deficiency i children causes retarded growth, poor appetite, constipa tion, neuritic pains and tenderness.

Alcoholic psychoses are believed to be due, in par at least, to deficiency of this vitamin which is supposed t be responsible for the aggravation of any pre-existin cardiac disease and the precipitation of cardiac failur which is often observed in chronic alcoholism.

It follows therefore that any of these conditions will be benefited by the administration of the official preparations or by giving foods rich in this vitamin. It has also been found valuable in various types of neuritis, specially toxic neuritis, *e.g.* alcoholic, lead or arsenic ; vomiting of pregnancy ; atonic constipation, etc. In urgent and bad cases intramuscular or intravenous administration of some pure synthetic preparation may be given. Each ampoule of 1 mil contains 20 to 100 mg.

Its administration leads to improvement of acute leprous neuritis and has been successfully used in **infantile paralysis** (25 to 30 mg.) by injection.

Since its deficiency causes an increase of blood sugar and lactic acid indicating a disturbance of carbohydrate metabolism, it has been used in **diabetes mellitus** where it lessens the amount of insulin.

The amount of vitamin needed is proportional to the amount of food supplied, the body weight, the total metabolism, and the energy value of the ingested carbohydrate. Anything that increases metabolism, such as muscular work, fever, pregnancy or hyperthyroidism, increases the amount of this vitamin requirement. A diet rich in fat has a sparing action on the vitamin B_1. An adult requires about 1 mg. of aneurine daily and more during pregnancy and childhood. The body does not store this vitamin and the excess over immediate requirements is excreted by the urine.

It may be administered by the mouth in the form of solution or tablet, or may be administered by subcutaneous, intramuscular or intravenous injection. The daily requirement of this vitamin according to Cowgill is 10 *i.u.* (*i.e.* 30 micrograms) per 100 calories of food intake.

Cowgill's formula :—

Aneurine requirements = Body weight in kg. × calorie requirement × 0.0000284.

The Unit of Antineuritic Activity (Vitamin B_1) is defined as the specific antineuritic activity contained in 3.125 mcgrm. of the Standard Preparation.

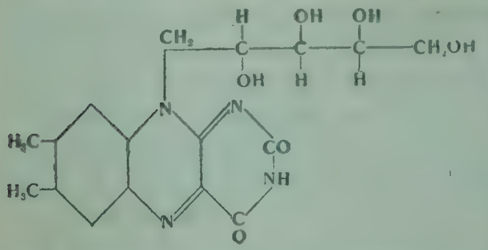
Vitamin B_2 Complex is composed of two factors: *Riboflavin*, which is responsible for the growth promoting properties ; and *Nicotinic acid*, which is pellagra preventive, also known as P-P of Goldberger.

RIBOFLAVINA. (Riboflav.). **Syn.**—Lactoflavin.—Riboflavine is 6 : 7-dimethyl-9-(*d*-1'-ribityl)-*iso*alloxazine. May be obtained from yeast and other natural sources or by synthesis.

Characters.—An orange-yellow, crystalline powder ; odour, slight ; taste, slightly bitter ; slightly soluble in water.

B. P. Dose.—Prophylactic (daily) :—1/60 to 1/16 gr. or 1 to 4 mg. Therapeutic (daily) :—1/12 to 1/6 gr. or 5 to 10 mg.

Riboflavin is a water soluble pigment first isolated from milk (lactoflavin), also found in yeast and liver extract. It has been synthesised and has the formula—$C_{17}H_{20}N_4O_6$. The phosphate of this pigment when conjugated with protein forms a flavoprotein which acts as a respiratory enzyme of the tissues. Best sources of riboflavin are yeast, rice polishings, liver, kidney, eggs, milk, cheese, wheat germ, cereals, carrots, green beans and peas, spinach and tomatoes.

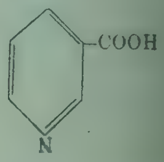


It appears to be essential for the maintenance of normal fat metabolism, and its deficiency causes cataract, cheilosis and degenerative changes of the spinal cord and peripheral nerves, stomatitis and glossitis. There is evidence that the lack of this vitamin may be associated with ocular manifestations like photophobia, dimness of vision and impairment of visual acuity, congestion of the sclera, corneal opacity, abnormal pigmentation of the iris and interstitial keratitis.

Its deficiency is often associated with aneurine and nicotinic acid deficiencies.

It is used in conditions characterised by lesions of the tongue, lips, ocular manifestations and the dermatitis of pellagra. Daily requirement for an adult is from 1.8 to 3 mg. but is greater during pregnancy and lactation.

ACIDUM NICOTINICUM. **Syn.**—Pelonin.—Nicotinic Acid is pyridine-3-carboxylic acid, and may be obtained from nicotine by the action of a suitable oxidising agent. White or creamy-white crystals or crystalline powder; odourless; taste, feebly acid. *Soluble* in 75 parts of water at 15°C.; readily in boiling water and alcohol (95 p.c.); soluble in solutions of alkalies.



B. P. Dose.—Prophylactic (daily) :—**1/4 to 1/2 gr.** or **15 to 30 mg.** Therapeutic (daily) :—**3/4 to 4 grs.** or **50 to 250 mg.**

Official Preparation

1. **Tabellae Acidi Nicotinici.**—**B. P. Dose.**—Prophylactic (daily) :—**1/4 to 1/2 gr.** or **15 to 30 mg.** Therapeutic (daily) :—**3/4 to 4 grs.** or **50 to 250 mg.** N. B. When the quantity in each tablet is not stated, 3/4 gr. tablets shall be supplied.

Nicotinamidum. **Syn.**—Nicotinic Acid Amide; Niacinamide.—Nicotinamide is pyridine-3-carboxylic acid amide. Prepared by the action of thionyl chloride on nicotinic acid. In white, crystalline, almost odourless powder. Taste, bitter. *Soluble* in 1 part of water, about 1.5 parts of alcohol (95 p.c.).

B. P. Dose.—Prophylactic (daily) :—**1/4 to 1/2 gr.** or **15 to 30 mg.** Therapeutic (daily) :—**3/4 to 4 grs.** or **50 to 250 mg.**

Official Preparations

1. **Tabellae Nicotinamidi.** *Syn.—Tablets of Nicotinic Acid Amide.*—**B. P. Dose.**—Prophylactic (daily) :—**1/4 to 1/2 gr.** or **15 to 30 mg.** Therapeutic (daily) :—**3/4 to 4 grs.** or **50 to 250 mg.** N. B. When the quantity in each tablet is not mentioned, 3/4 gr. tablet shall be supplied.

2. **Injectio Nicotinamidi.** *Syn.—Niacinamide Injection.*—**B. P. Dose.**—**3/4 to 4 grs.** or **50 to 250 mg.** *daily.* N. B. When no strength is stated, a solution containing 3/4 gr. in 15 ms. shall be supplied.

Nicotinic acid plays an important role in the enzyme systems of the body and is related to carbohydrate metabolism. Its deficiency produces mild psychic disturbances,

neurasthenic symptoms, transient delusion leading to an 'encephalopathic syndrome' with delirium, delusion and stupor.

Nicotinic acid used in animals in large doses produces cumulative effects giving rise to intestinal irritation and possibly convulsive signs. It is several hundred times less toxic than nicotine and does not possess any action on the autonomic nervous system. In therapeutic doses it causes transient vaso-dilatation specially marked over the blush area and may be accompanied by itching and burning. Peripheral blood flow may be increased. These effects are not observed with nicotinamide which has the same vitamin activity as the acid.

Both the acid and the amide are used for the prevention and treatment of **pellagra** and in sub-pellagroid condition manifested by indigestion, irritability, burning of the skin, forgetfulness and insomnia. By their use glossitis and stomatitis and the mental symptoms are rapidly improved. It is better when treating pellagra patients to administer other factors of vitamin B complex, specially riboflavin. Nicotinic acid is generally administered in doses 0.1 grm. (1½ grs.) five times a day in the form of tablets or may be given by injection in doses of 10 to 20 mg. (1/6 to 1/3 gr.). Since nicotinic acid causes disappearance of porphyrin in the urine of pellagrins, it has been used in the treatment of other conditions in which porphyrinuria occurs. Roy has shown that nicotinic acid when administered with LD. 50 of sulphanilamide (5.5 G./Kg.) to rats, reduced mortality to a significant extent and limited the occurrence of severe toxic reactions.* Thus it has been used with benefit in the treatment of the toxic symptoms which sometimes follow the use of sulphonamide compounds, or in radiation sickness. It has also been used in delirium tremens where very quick improvement is observed, in Vincent's angina, and in the glossitis which may occur in diabetics undergoing insulin treatment.

Pellagra is now considered to be a mixed deficiency disease, a true "polyavitaminosis"; thiamine, riboflavin, nicotinic acid and often ascorbic acid are concerned.

It is also useful in psychotic disturbance of the aged, the debilitated, the arteriosclerotic and chronic alcoholics. It has been suggested that mental disturbances occurring in the alcoholics may be due to deficiency of nicotinic acid.

Caution.—Nicotinic acid sometimes produces flushing and tingling of the skin which however disappear soon, if not it may be necessary to suspend its use.

Para-Aminobenzoic Acid (PABA).—It is a white crystalline powder slightly soluble in water. Sodium salt is water-soluble. Its rôle in human economy is not known. It is fairly non-toxic and it

* B. B. Roy, Indian Medical Gazette, Dec. 1942, page 729.

has been suggested that it interferes in someway with the proliferation of rickettsial organism within tissue cells, probably by increasing cellular metabolism. It is present in the yeast and liver extract. *P*-aminobenzoic acid is an effective **antirickettsial agent** in scrub typhus, Rocky Mountain spotted fever and murine typhus, and also in **radiation sickness.** In order to be effective the blood levels should be determined daily which should be 30 to 60 mg. per 100 mils. It is generally used as sodium para-aminobenzoate. *Initial dose*, 4 to 6 grm., *subsequently*, 2 to 3 grm. every 2 hours. It may be administered by the mouth but since it is eliminated rapidly it is necessary to administer every 2 to 3 hours to maintain therapeutic blood levels. Parenteral administration is indicated when the patient cannot retain it due to vomiting or is in a comatose condition. Since *p*-aminobenzoic acid is antagonistic to sulpha-group of drugs, it is possible that its administration may counteract some of the toxic symptoms, specially **agranulocytosis,** which follow the use of these compounds.

NH_2

COOH

It is an effective antidote to carbarsone and certain other arsonates and protects against stibosan. It is generally injected three hours before administration of arsenic.

It has been found that it modifies the formation of melanin, the hair pigment and that it darkens the hair of grey-haired persons when given in 100 mg. doses twice a day for six to eight months.

Pyridoxine Hydrochloride. (Vitamin B_6). **Syn.**—Rat Achrodinia Factor.—It is a white crystalline powder stable in air and slowly affected by sunlight. 1 grm. dissolves in about 5 mils of water and in about 90 mils of alcohol.

Vitamin B_6 or pyridoxine is an essential factor in human nutrition and plays an important role in normal protein metabolism and its requirement is related to the amount of protein taken.

Deficiency of this vitamin causes dermatitis in young rats and may be one of the factors deficiency of which contributes to the syndrome complex of pellagra. It is also suggested that pyridoxine is normally responsible for the maturation of granulocytes and their delivery from the bone-marrow. In agranulocytosis maturation is arrested and delivery blocked. It has therefore been used as a powerful leucopoietic stimulant in **agranulocytosis.** It is administered in 10 p.c. solution in doses of 125 to 200 mg. daily for 5 to 6 days. Improvement is generally observed within 48 hours with return of normal granulocyte count. It has also been used in **hyperemesis gravidarum, morning sickness of pregnancy** and in **radiation sickness.** Usual dose being 30 to 100 mg. (1/2 to 1½ gr.) orally, intramuscularly or intravenously. In doses of 50 to 100 mg. (3/4 to 1½ gr.) by mouth or intravenously it has been used in **myasthenia gravis, muscular dystrophy** and **paralysis agitans.** Treatment being continued for three weeks.

Pantothenic Acid.—It is available as Sodium and Calcium Pantothenates. It is present 33.3 microgram per 100 mils of blood of normal person. Its richest sources are, yeast, liver, eggs, pea nut, and whole wheat. Its role in the human has not been established. With *p*-aminobenzoic acid and biotin it shares the effect of restoring grey hair to normal colour. Daily requirement is 5 to 10 mg. Its administration produces some improvement in **peripheral neuritis, Korsakoff's syndrome** and **delirium tremens.** It is used in the form of **Calcium Pantothenate,** *Dose,* 0.15 grm. (2½ grs.) by mouth daily.

Biotin, formerly known as Vitamin-H, is found in close association with other members of vitamin-B complex. The chief sources are yeast, liver, eggs, peas and cereals. It is an essential growth factor of many bacteria and moulds and its deficiency in

man is characterised by exfoliative dermatitis, greyish pallor of the skin, atrophy of the lingual papillae, disturbed erythropoiesis and spasticity.

Inositol is also known as alopecia vitamin as its deficiency in animals results in falling of hair, but it is doubtful. It is believed to be a factor for growth and health and for fat metabolism.

SACCHAROMYCES SICCUM, I.P.L. **Syn.**—Faex Medicinalis; Cerevisiae Fermentum.—Dried Yeast consists of the dry cells of any suitable strain of *Saccharomyces cerevisiae*, or *Torula utilis*.

Characters.—Yellowish white or pale yellowish orange flakes, granules or powder; containing numerous irregular masses and isolated yeast cells. Odour and taste, characteristic.

Composition.—Several enzymes; (1) *Zymase*, which decomposes monosaccharides into alcohol and CO_2; (2) *Invertase*, which inverts sugar; (3) *Maltase*, converts maltose into dextrose; and (4) *Endotryptase*, a proteolytic enzyme. Fats, ergosterol, various carbohydrates and various proportions of proteins combined with nucleic acid forming nucleins and nucleo-proteins; (5) *Water soluble vitamin B complex*.

Dose.—30 to 60 grs. or 2 to 4 grms.

PREPARATION

1. **Extractum Saccharomyces Siccum Concentratum, I.P.L.**—Obtained by concentrating in *vacuo* an aqueous or 0.1 p.c. acetic acid extract of dried yeast, to a pasts consistence. Contains in each grm. 150 micrograms of aneurine hydrochloride; 60 micrograms of riboflavin; and 500 micrograms of nicotinic acid. A dark brown viscous liquid. *Dose.*—15 to 30 gr. or 1 to 2 grm.

PHARMACOLOGY AND THERAPEUTICS

The action of yeast is that of nuclein and it is both a **leucocyte-stimulant** and **bactericide.** Both brewer's and compressed yeast are gastro-intestinal antiseptics; they increase intestinal peristalsis, clear the tongue and aid in combating infections. Dried yeast contains not less than 40 p.c. of protein and in each gramme equivalent of not less than 12 micrograms of aneurine hydrochloride, 40 micrograms of riboflavin, and 250 micrograms of nicotinic acid.

Being rich in *vitamin B complex* yeast is used in **beri-beri.** It may be used either with meals or on an empty stomach, suspended in water or orange juice. The yeast-cake may be used in solution in water; the dose being half to one-third of a cake. It may also be administered either in the crude form as obtained from the brewers, or as **Marmite.** Because of the presence of ergosterol, yeast, when irradiated with ultra-violet light, acquires anti-rachitic properties from the conversion of ergosterol into vitamin D.

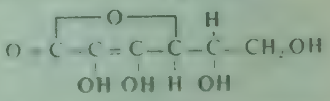
The use of marmite has been extolled in the treatment of **macrocytic hyperchromic anaemia,** specially the anaemia of pregnancy. Since dried yeast, or watery extract of yeast is therapeutically inactive as a source of Castle's extrinsic factor, but autolysed yeast products are active, it has been suggested that the principle in yeast active in the treatment of tropical macrocytic anaemia is identical **with the extrinsic factor.**

ACIDUM ASCORBICUM

Ascorbic Acid. (Acid. Ascorb.)

Syn.—Vitamin C; The Antiscorbutic Factor; Cevitamic Acid.

Source.—Ascorbic Acid is the enolic form of 3-keto-*l*-gulofuranolactone. Obtained from the ripe fruit of *Capsicum annum* and other vegetable sources, or by synthesis. Contains not less than 98 p.c. of $C_6H_8O_6$.



Characters.—Minute colourless crystals; odourless; taste, acid, resembling that of lemon juice. Readily soluble in water; soluble in alcohol (95 p.c.), in absolute alcohol, and in acetone. Insoluble in solvent ether.

Storage.—It is stable when kept in a glass bottle. Solution of ascorbic acid, especially if alkaline, deteriorates rapidly in contact with air.

B. P. Dose.—*Prophylactic (daily)* : 2/5 to 1¼ gr. or 25 to 75 mg. *Therapeutic (daily)* :—3 to 8 grs. or 0.2 to 0.5 grm.

Official Preparation

1. Tabellae Acidi Ascorbici. *Syn.—Tablets of Vitamin C.* B. P. Dose. Prophylactic (daily) : 2/5 to 1¼ gr. or 25 to 75 mg. Therapeutic (daily) : 3 to 8 grs. or 0.2 to 0.5 grm. N. B. If the quantity in each tablet is not stated, 3/4 gr. tablet shall be dispensed.

Vitamin C is water-soluble and its richest sources are cabbages, turnips, lemons, oranges and tomatoes. It is less widespread than vitamin B but is more sensitive to heat and drying. It has been isolated in the pure form from fruit juice, and has also been synthetically prepared.

Most animals, can manufacture ascorbic acid ; hence they are independent of any supply with food. But man, monkey and guinea-pig require their supply with food or they die from disease. It is found in large quantities in the suprarenal cortex where it is possibly synthesised. Although it is present in fresh milk, it is destroyed by pasteurization (about 150°F.) or by drying. Salting of fish preserves this vitamin.

A pint of average commercial milk contains about 5 mg. and fresh raw milk contains about 14 mg. of vitamin C. Fresh orange and lemon juice contains 65 to 130 mg. per 100 mils (3½ ozs.).

Daily human requirement of ascorbic acid is 50 to 75 mg. To prevent symptoms of pre-scorbutic condition, children should get about 50 mg. daily. In bacterial infection the intake should be 100 to 200 mg. and during pregnancy and lactation, a minimum of 100 mg. daily.

Its deficiency leads to malnutrition with loss of weight and eventually symptoms of scurvy. It has also been claimed that its absence produces dental caries, anaemia, anorexia and various forms of infection. It regulates the intracellular substances of capillaries ; promotes the growth and ripening of the red and white blood cells ; and with vitamin D regulates calcium metabolism. Due to interference with tissue regeneration its deficiency is an important factor in delaying healing of wounds and McConkey and Smith have shown that peptic ulcer is apt to occur in animals when in a state of vitamin C deficiency. Its deficiency produces subcutaneous haemorrhage, degeneration of skeletal muscle and necrotic foci in the liver.

It is however doubtful if capillary fragility is due to deficiency of ascorbic acid or to vitamin P which is also present in citrus fruit.

Microcytic anaemia is frequently present with scurvy and the haemorrhage which tends to produce anaemia is cured by ascorbic acid. It is also essential for the maturation of red blood cells and converts ferric salts into ferrous. It is also effective in methaemoglobinaemia.

Administration of ascorbic acid not only prevents but also helps to cure infantile and adult **scurvy.** In mild

cases administration of foods rich in this vitamin, *e.g.* lemon juice, oranges, etc., will cause improvement. But in severe cases ascorbic acid should be given, and if necessary hypodermically or intravenously. As the solution is acid with a pH of about 2.5 it will cause local necrosis with sterile abscess when given hypodermically, and haemolysis when given intravenously. It should be given dissolved in normal saline solution (50 to 100 mg. in 5 mils) and neutralised immediately before use with half its weight of bicarbonate of soda.

Ascorbic acid has been used in chronic lead poisoning. It unites with the toxic lead ions to form a poorly ionised and much less toxic compound which is probably absorbed by the liver and passed into the bile and excreted with the faeces. It has been used in **dermatitis** which follows use of arsenic compounds and other heavy metals.

It has been claimed that large amounts of ascorbic acid lessen the anaphylactic shock from injection of antitoxic sera in susceptible persons. It has further been suggested by Meyer that it stops the growth of pneumococci and streptococci and apparently raises the phagocytic value of human blood. It is therefore one of the necessary factors for resisting infection.

It has been used in peptic ulcer, capillary bleeding, asthma, allergic conditions, psoriasis, rheumatoid arthritis, sulphonamide poisoning and whooping cough.

Vitamin P.—It is a water-soluble crystalline substance of the flavone group called hesperidin or citrin, and occurs naturally with ascorbic acid, *e.g.* in lemon juice. It is concerned in the maintenance of capillary impermeability and has been used in haemorrhagic diseases. Its existence is doubtful.

Rutin is a yellow crystalline glycoside derived from buckwheat or tobacco and is closely related chemically to hesperidin supposed to be vitamin P. It lowers **capillary fragility** and has no effect on blood pressure. It is used as an antihaemorrhagic factor in hypertension with tendency to haemorrhage, and as a preventive in retinal and cerebral haemorrhage. It is also useful in the treatment **hypertesion** with thiocyanate to offset the tendency of the latter drug to increase capillary fragility, also used to arrest progress of diabetic retinitis and as a pre-operative and post-operative measure to **reduce post-operative haemorrhage. Dose.**—20 mg. or 1/3 gr. three times daily by the mouth. May be given in doses of 60 to 300 mg. (1 to 5 gr.) when there is deficiency of ascorbic acid or may be combined with it.

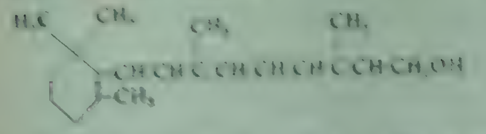
2. Fat Soluble Vitamins

VITAMIN A

Syn.—Growth Promoting Factor; Anti-infective Factor; Fat-soluble A.

Source and Characters.—It is present in the yellow pigment of plant and occurs in the form of pale yellow needles, and it is known to be formed in the animal body from the carotenoid pigment ß-carotene. Carotene is a hydrocarbon, and occurs in three forms, *viz.*,

alpha, beta and gamma carotene, and cryptoxanthine, a clo related pigment found in ye maize.



Human requirement of vi min A daily is 2,000-4 units for adults; 6,000 s units for children; and 5 units for pregnant women. The amount is estimated by the co reaction with antimony trichloride which gives a blue reaction.

Liquor Vitamini A Concentratus.—It is a solution of vitami containing in 1 grm. 50,000 *Units of vitamin A activity.* It m consist of a suitable fish-liver oil or blend of fish-liver oils or p pared by dissolving, at a temperature not exceeding 60° C., a sou of vitamin A in a suitable vegetable oil, such as arachis oil.

Characters.—A pale yellow or yellow oily liquid with a faint but not ra odour. Taste bland or slightly fishy. Slightly soluble in alcohol (95 p.c.), misc with solvent ether.

B. P. Dose.—1 to 10 ms. or 0.06 to 0.6 mil. **Dose in Units.**—2500 to 25, units, daily.

Oleum Selacheidei. I.P.I.—Shark-liver Oil is the oil obtai from fresh or carefully preserved livers of the various species shark. Contains in 1 grm. not less than 6,000 i.u. of vitamin activity.

Characters.—A pale-yellow or brownish-yellow oil; odour fishy but not ranc taste, bland and fishy. Slightly soluble in alcohol (90 p.c.).

Dose.— 3 to 15 ms. or 0.2 to 1 mil. Vitamin A, 1500 to 7500 Units (appro mately).

PREPARATION

1. **Extractum Malti cum Oleo Selachoidei, I. P. I.**—Ext. Malt 950 grm Shark-liver oil 50 grms. Contains not less than 5 p.c. w/w of shark-liver oil a not less than 200 i. u. of vitamin A per grm. Dose.—60 to 240 ms. or 4 to 16 m

Vitamin A is absorbed from the gastro-intestinal tra and this depends upon the condition of the intestinal tra and the presence of oils in the gut. It is stored in the live

Vitamin A is essential for maintaining the integri of the epithelial linings throughout the body and the prop structure and function of the nervous system. Its defic ency (*a*) retards growth and lowers resistance, either loc or general, to bacterial infections; (*b*) causes xerophtha mia or inflammation of the eye; (*c*) retards regenerati of the visual purple and helps development of night blin ness; (*d*) decreases the number of blood platelets; (produces atrophy of the cells of the salivary gland mucous membrane of the intestine and of the intestin villi; (*f*) causes dryness of the skin due to keratinisati of epithelial tissues, and a tendency to papular eruption (*g*) causes paralysis of various types from demyelinati of the spinal cord; and (*h*) helps formation of phospha calculi. It is antagonistic to thyroxine, an excess of whic as in hyperthyroidism, causes depletion of vitamin storage.

Mellanby has suggested that the paralysis associat with famine, *e.g.* convulsive ergotism, may be the res of the absence of this vitamin (see page 430).

Vitamin A administered orally increases renal blo flow, filtration rate and maximal tubular excretion in hype

[illegible] subjects and has been used in the treatment of **hypertension.** While some observers reported lowering of pressure, others found it ineffective. Further work in this direction is necessary.

The main sources of this vitamin are (*a*) certain fats of animal or vegetable origin; and (*b*) chlorophyll in green vegetables. Vegetable oil rich in this vitamin is red palm oil. Green vegetables and carrots contain no vitamin A, but have the same physiological action, as the animal body can convert a part or whole of carotene into vitamin A. Since the fat soluble vitamin is stored in the liver, liver oils, specially fish liver oil, and shark-liver oil contain this vitamin in a concentrated form. It is found in abundance in cream, butter, beef fat, mammalian liver and yolk of eggs. Milk does not lose this vitamin by boiling or pasteurising, but when evaporated by vacuum or aeration method it is destroyed.

Vitamin A contents of certain foods :—

Milk 1 pt., butter 1 oz., carrots (fresh or boiled) 1/2 lb., cabbage (fresh or boiled) 1/4 lb. = 2000 units; one egg of 20 grammes = 600 units; cod-liver oil per dr. = 200 to 5000 units; halibut-liver oil per drop (20 mg.) = 600 to 1200 units.

VITAMIN D

It is a fat-soluble vitamin with antirachitic properties and spilts up into D_1, D_2, and D_3, all of which have been shown to possess antirachitic properties. Of these vitamin D_2 has been recognised under the name "Calciferol." They are all sterol compounds and are therefore related to the male and female sex hormones (*see* page 448) and to many of the cardiac glycosides.

It occurs mostly with vitamin A and at one time it was considered to be the same. It is found in abundance in cod-liver oil, halibut-liver oil and other fish oils. It is also present in milk, cheese, meat, butter, yolk of eggs. In the body it is formed by the action of ultra-violet rays or direct sunlight on the skin. Similarly, it is prepared by the action of ultra-violet rays on ergosterol, milk, yeast and other foods.

Deficiency of this vitamin causes rickets and defective calcification of teeth from lack of absorption of calcium or phosphorus. It increases the power of the blood to carry more calcium and phosphorus in balanced proportions to be deposited on the bones. It is possible that it helps absorption of calcium by reducing the alkalinity of the intestinal contents by forming soluble calcium soap or acid calcium phosphate. Cohn and Greenberg have demonstrated that besides promoting absorption it exerts a direct influence on the mineralization of bone in rachitic animals.*

It was thought that the action of this vitamin depended upon the integrity of the parathyroid glands. It is however now believed that it increases the serum calcium by promoting absorption from the intestine, whereas para-

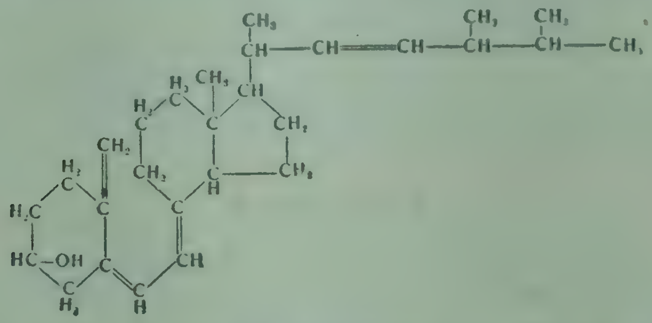
*Jour. Biol. Chem. 1939, 130, 625.

thyroid extract raises blood calcium by mobilising calcium and phosphate from the soft tissues and bones.

Parathyroid hormone and vitamin D used for a prolonged period produce hypercalcaemia, the former by drawing calcium from the bones while the latter by increasing absorption of calcium and at the same time reducing its excretion by the kidneys.

CALCIFEROL. $C_{28}H_{43}OH$.—Calciferol is prepared by the ultra-violet irradiation of ergosterol in a suitable solvent. 1 milligram contains 40,000 Units *of antirachitic activity (vitamin D).*

Characters.—Colourless, acicular crystals; odourless. *Insoluble* in water; readily soluble in alcohol (95 p. c.), in solvent ether, in chloroform, and in acetone; soluble in 50 to 100 parts of vegetable oils.



Storage.—It should be stored in hermetically sealed glass containers, from which air has been evacuated or replaced by an inert gas, protected from light and stored in a cool place.

B. P. Dose.—*Prophylactic (daily) for infants and adults* :—**1/2400 to 1/600 gr. or 0.025 to 0.1 mg. (1000 to 4000 Units).** Therapeutic (daily) for infants and adults :—**1/1200 to 1/120 gr. or 0.05 to 0.5 mg. (2000 to 20,000 Units).**

OFFICIAL PREPARATIONS

1. **Liquor Calciferolis.**—It is a solution of calciferol in oil. Contains in 1 grm. 3000 Units of antirachitic activity (vitamin D). **B. P. Dose.**—Prophylactic (daily) for infants and adults :—**5 to 20 ms. or 0.3 to 1.2 mils. (1000 to 4000 Units).** Therapeutic :—**10 to 100 ms. or 0.6 to 6 mils. (2000 to 20,000 Units)** daily.

2. **Liquor Vitamini D Concentratus.**—A solution of vitamin D containing in 1 grm. 10,000 units of antirachitic activity (vitamin D). Prepared in the same way as concentrated solution of vitamin A. **B. P. Dose.**—Prophylactic :—**1½ to 6 ms. or 0.1 to 0.4 mil. (1000 to 4000 Units)** daily. Therapeutic :—**3 to 30 ms. or 0.2 to 2 mils. (2000 to 20,000 Units)** daily.

3. **Liquor Vitaminorum A et D Concentratus.**—It is a solution containing in 1 grm. 50,000 units of vitamin A activity, and 5,000 units of antirachitic activity (vitamin D). It may consist of a suitable fish-liver oil or blend of fish-liver oils, or prepared by dissolving at temperature not exceeding 60°C. a source of vitamin A and vitamin D in a suitable vegetable oil, such as arachis oil. **B. P. Dose.**—**1 to 10 ms. or 0.06 to 0.6 mil.** Dose in Units :—Vitamin A, **2500 to 25,000** Units; **Vitamin D, 250 to 2500 Units** daily.

USES.—The utility of vitamin D has been fully discussed, calciferol possesses antirachitic property of great power. It favours the absorption of calcium and the retention of bone-forming salts in the body. In rickets the calcium and phosphorus are absorbed but the body is not able to deposit them on the bones, and these are re-excreted so that a negative balance results. Administration of calciferol or liquor vitamini D concentratus prevents this loss, and it is possible that it helps not only the absorption of calcium by altering the reaction of the gut to acid. but

also retention of the bone forming salts. The different liquid preparations are therefore used not only for the treatment of **rickets** but also as a prophylactic for children living under conditions of malnutrition and who are deprived of fresh air and sunlight. Just as rickety children improve under vitamin D, similar improvement follows when these children are exposed to direct sunlight or to the artificial ultra-violet rays. Calciferol or food rich in vitamin D will also improve the condition known as **osteomalacia** from which women often suffer due to repeated pregnancy and lactation and want of proper food, fresh air and sunlight. Vitamin D may also be used with benefit during the period of **pregnancy** and **lactation.** Children showing defective growth and nutrition and those suffering from caries of the teeth are benefited by its use. Since it helps absorption of calcium it is necessary that some form of calcium should be given with it. Good results have been reported from large doses (200,000 to 600,000 Units daily) in **rheumatoid arthritis, psoriasis** and various **allergic** states.

Natural vitamin D as found in fish oils is more potent in facilitating calcification than calciferol, which is chemically related to ergosterol, while natural D factor is related to cholesterol.

Hypervitaminosis.—In moderate doses there is hypercalcaemia at growing ends of the bones and a corresponding diminution of calcium and phosphate in the intestine. In severe poisoning calcium and phosphate may be drawn from bones. Deposits of calcium takes place in the vessels, heart, stomach, colon, kidneys and lungs with formation of calcium phosphate calculi. Toxic symptoms are anorexia, nausea, vomiting, diarrhoea, loss of weight, malnutrition, fever and nephritis. Spleen and the thymus are atrophied, and the animal loses weight rapidly and dies.

OLEUM MORRHUAE

Cod-liver Oil. (Ol. Morrh.)

Syn.—Oleum Jecoris Aselli. *Macher tel*, Beng. *Machlika tel*, Hind.

Source.—Obtained from the fresh liver of the cod, *Gadus morrhua*, and other species of *Gadus*, and freed from solid fat by filtration at about 0°C. It contains in 1 grm. not less than 600 Units of vitamin A activity, and not less than 85 Units of antirachitic activity (vitamin D).

Characters.—A pale yellow liquid ; odour, slight, but not rancid ; taste, bland or slightly fishy. Slightly *soluble* in alcohol (90 p. c.) ; miscible with solvent ether, with chloroform, and with light petroleum.

Composition.—The chief constituents are *Vitamins A* and *D*, also (1) Glycerides of unsaturated acids chiefly docosahexenoic acid. (2) Free *fatty acids* (palmitic, stearic). (3) Traces of *cholesterol* and *bile acids*. (4) Trace of *iodine*.

B. P. Dose.—60 to 180 ms. or 4 to 12 mils in divided doses daily.

Official Preparations

1. **Extractum Malti cum Oleo Morrhuae.**—Contains about 72 ms. of cod-liver oil in 1 oz. **B. P. Dose.—60 ms. to 1 oz. or 4 to 30 mils** daily in divided doses.
2. **Emulsio Olei Morrhuae.**—Cod-liver oil 50 p. c. **B. P. Dose.—120 to 360 ms. 8 to 24 mils daily in divided doses.**

PHARMACOLOGY

Externally.—Cod-liver oil is a bland unirritating oil freely absorbed through the skin.

Internally. **Gastro-intestinal tract.**—Cod-liver oil is rapidly absorbed and digested because the unsaturated fatty acids it contains facilitate its emulsification and saponification by its admixture with the alkaline secretions of the pancreas, the intestinal glands and the bile. But on account of its fishy unpleasant smell, many patients cannot retain it, and with some it causes indigestion. In large doses, it may cause diarrhoea, the oil being expelled in the stools.

Metabolism.—Cod-liver oil is not only quickly absorbed and readily assimilated but enters into permanent combination with the body cells yielding energy to them. It is therefore a **food** ; a tablespoonful yielding about 130 calories. But the specific action of cod-liver oil depends upon the unsaturated fatty acids which serve the immediate needs in the production of energy ; the saturated acids are stored in the nature of reserve. It has been suggested that the unsaturated acids enter the fatty envelop of the tubercle bacilli and kill them. The value of cod-liver oil is due to the presence of vitamins A and D which are essential for the nutrition and growth of young animals, and for correcting improper balance of calcium and phosphorus intake. Moreover, the unsaturated fatty acids and vitamin D help absorption of calcium (*see* page 98). The true vitamin factor is contained in the 1 p.c. of the non-saponifiable matter contained in the oil.

Elimination.—It is mostly absorbed, a little is expelled in the faeces. Some of the acid ingredients escaping through the skin may produce a sort of acne.

THERAPEUTICS

Externally.—Inunction is a good method for introducing the oil into the system. Wasting diseases of children are specially benefited by this method, the only drawback being its objectionable odour. It has been used as a local application in burns, ulcers refusing to heal and diabetic gangrene. It is claimed that the oil is bacteriostatic as well as bacteriolytic and stimulates granulation and epithelization.

Internally.—Cod-liver oil is valuable in all sorts of chronic wasting diseases especially in scrofulous disease in its various forms, and phthisis, caries of bones, chronic joint disease, long-continued suppuration, chronic bronchitis, general debility due to underfeeding, exhaustion, overwork, etc. Convalescence from acute illness, *e.g.* pneumonia, etc., is benefited under its use.

Being rich in vitamin A and D it is pre-eminently suited for promoting growth and nutrition, and preventing **rickets** and defective calcification of teeth. For the same reason it is useful for prevention and cure of **osteomalacia.** As it contains iodine (0.00001 p.c.) its use has been suggested in the treatment of goitre, which is supposed to be due to deficiency of iodine in the food.

Contra-indications.—Indigestion, nausea, vomiting, eructation, diarrhoea, gastric catarrh, high temperature, and severe haemoptysis contra-indicate its use.

Prescribing hints.—It should be commenced with small doses, say 30 ms. and gradually increased to 90 ms. and given after food twice or thrice daily. In the beginning, say for one week, it is a good plan to give only one dose a day preferably after dinner.

Brown oil is superior to pale oil because it contains more fatty acids but its disagreeable smell and taste are a drawback. Children generally can take it better, or soon get accustomed to its taste, but in the majority of cases a pleasant combination becomes necessary. Saponification should be avoided on account of the chemical changes that would occur with the fatty acids contained in the form of glycerides. In fact the great *point is to preserve these acids unchanged.* It can also be given in flexible capsules, mixed with isinglass jelly, or still better with extract of malt. Some patients prefer to take it on milk, coffee, wine or orange juice. A pinch of salt placed on the tongue, a cut lemon sucked, a piece of fresh ginger well chewed, and some of the juice swallowed before and after the dose effectively remove the nauseous taste.

OLEUM HIPPOGLOSSI. (Ol. Hippogloss.). Halibut-liver Oil. —A fixed oil extracted from the fresh or suitably preserved, liver of the halibut, *Hippoglossus hippoglossus.*

Characters.—A pale to golden yellow liquid ; odour, fishy, but not rancid ; taste, fishy. Slightly soluble in alcohol (90 p. c.) ; miscible with solvent ether, with chloroform, and with light petroleum.

B. P. Dose.—1 to 8 ms. or **0.06 to 0.5 mil.** Vitamin A ; **1500 to 12,000 Units.** N. B. The vitamin D activity varies between 2500 and 3500 Units per grm.

ACTION AND USES

Halibut-liver oil contains vitamin A activity from 15,000 to 250,000 units in each gramme. The vitamin A content as measured by the blue unit test is fifty times greater than cod-liver oil, while that of the vitamin D content varies from 2500 to 3500 units per grm. It is largely used in place of cod-liver oil and is free from any strong and unpleasant taste. *Two to three drops provide the vitamin equivalent of a teaspoonful of cod-liver oil.*

Dihydrotachysterol. (Not official).—It has been pointed out that although ergosterol possesses no antirachitic property, its irradiation by ultra-violet rays produces a series of compounds with different pharmacological action. Of the series, calciferol is powerfully antirachitic, while another product of irradiation is tachysterol. A reduction product of this compound, dihydrotachysterol, as also tachysterol resemble in their action parathyroid hormone. Dihydrotachysterol also to a certain extent promotes the absorption of calcium. Both types of action are useful in the treatment of **hypocalcaemia.** It is effective in controlling convulsions and in maintaining a normal calcium level in the blood. It can be used in all cases

where parathyroid is indicated and should be prescribed with calcium and vitamin D.

It is administered in doses of 2 to 8 mg. daily by mouth.

It is not a harmless drug and attention should be paid to the calcium and phosphorus levels of the blood. Over doses may cause polyuria, thirst, nausea, abdominal cramps and vertigo.

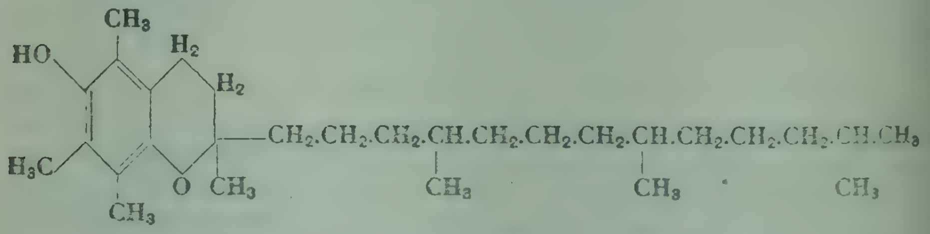
VITAMIN E

Syn.—Antisterility Vitamin ; Reproductive Vitamin.

It is a fat-soluble vitamin, and Evans has shown that it is necessary for reproduction and that its absence in the food causes death of the products of conception. Although observations were made on female rats, it has recently been reported that administration of wheat-germ oil to women with history of sterility conceived, and those with history of repeated abortion gave birth to normal living children. It is supposed to be one of the factors which hold oestrogen in equilibrium during pregnancy and possibly acts through the intermediary of the anterior pituitary. In the male its absence causes premature degeneration of the spermatogenetic cells, and sterility ; while in the female its absence causes sterility.

It is present in most animal tissues but not to a high degree and is absent in cod-liver oil. It is found in abundance in the embryos of seeds and green vegetables, chiefly lettuce, cotton seed, maize, peas, oats, corns and wheat-germ oil. It has been isolated in a crystalline form under the name of *Tocopherol* having the formula $C_{29}H_{50}O_2$.

Tocopherylis Acetas, B. P. C.—Tocopheryl Acetate is the acetate of natural α-tocopherol, which may be obtained from wheat-germ oil.



Dose.—1/20 to 1/6 gr. or 3 to 10 mg. Tablets containing 3 mg. (1/20 gr.) are sold under the name of **Ephynal.**

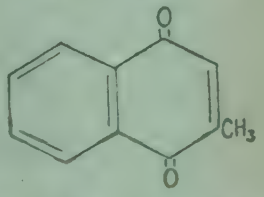
Phytopherol.—Capsules containing 3 ms. of an oily concentrate equivalent to 3 mg. of *dl*-α-tocopherol.

ACTION AND USES.—Vitamin E in any of the above forms has been used in the treatment of premature labour, habitual and threatened abortion, premature separation of placenta, certain cases of toxaemia of pregnancy, vulvo-vaginitis, dysmenorrhoea and to correct inadequate lactation. It is necessary for the integrity of voluntary muscle and its deficiency results in spastic paralysis. It has been used in **muscular dystrophies, amyotrophic lateral sclero-**

sis and **tabes dorsalis** with some improvement of muscular wasting and general condition and mental outlook. It has also been found to be of value in early and moderately advanced cases of **Dupuytren's contraction** and **fibrositis.** The optimal dose is 100 mg. three times a day until maximal improvement occurs, generally after four week's treatment. The maintenance dose is 1 mg. per kg. of body weight. No untoward effects have been observed after oral administration of three to four years.

Vitamin K.—"Koagulation" Vitamin.—It is a fat-soluble vitamin first found in the liver oils by Dam and Schonheyder necessary for the coagulation of the blood. It occurs in two-forms, *viz.*, vitamin K_1 and vitamin K_2. The former is 2-methyl-3-phytyl-1 : 4-naphthaquinone. It is a yellow oil and has been synthesised. It is not absorbed from the intestine in the absence of bile acids and the symptoms may arise either from this cause or from deficiency of this vitamin in the diet. It plays an important role in the formation of prothrombin and its deficiency prolongs the clotting time. It is found in green leaves of alfalfa, cabbage and spinach ; in strawberry and tomato ; soya bean and wheat-germ. It can also be prepared from fish-meal, rice bran or casein provided these are allowed to putrefy.

MENAPHTHONUM. (Menaphthon.). **Syn.**—Menadione ; Kapilon ; Prokyavit.—Menaphthone is 2-methyl-1 : 4-naphthaquinone.



Characters.—A bright yellow, crystalline powder. Odour, faint and characteristic : irritating to mucous membranes and skin ; decomposes on exposure to sunlight, darkening in colour to light brown. *Insoluble* in water, slightly soluble in alcohol (95 p. c.).

B. P. Dose.—1/60 to 1/12 gr. or 1 to 5 mg. by intramuscular injection daily.

Official Preparation

1. **Injectio Menaphthoni.**—**B. P. Dose.**—1/60 to 1/12 gr. or 1 to 5 mg. by intramuscular injection daily. N. B. When no strength is mentioned, 1/12 gr. in 15 ms. shall be supplied.

Acetomenaphthonum. Syn.—Kapilon Oral.—Acetomenaphthone is 1 : 4-diacetoxy-2-methyl-naphthalene. A white crystalline powder. Odourless or with a slight odour of acetic acid. Almost *insoluble* in water.

B. P. Dose.—1/30 to 1/6 gr. or 2 to 10 mg.

Official Preparation

1. **Tabellae Acetomenaphthoni.**—**B. P. Dose.**—1/30 to 1/6 gr. or 2 to 10 mg. N. B. If the dose is not mentioned, 1/12 gr. tablets shall be supplied.

Action and Uses.—Menaphthone is chemically allied to vitamin K_1 and vitamin K_2 and is essential for the maintenance of a normal level of prothrombin in the blood plasma, and its deficiency prolongs the clotting time. Its chief use is in **obstructive jaundice** and **neonatal haemorrhage**, conditions associated with reduced prothrombin content of the blood. Haemorrhages due to lack of this

vitamin occur in obstructive jaundice since it is not absorbed in the absence of bile. Administration of vitamin K or any of the preparation will cause a rise of the prothrombin and stop haemorrhage. To secure prompt response it should be given by intramuscular injection and then followed by oral administration of acetomenaphthone. Menaphthone is of value in conditions in which faulty absorption of fat may lead to deficiency of vitamin K. It has been found very satisfactory in preventing **post-operative haemorrhage** when administered with bile salts, which help its absorption, by the mouth. In doses of 2 mg. (1/30 gr.) thrice daily before meals acetmenaphthone has been used with good results in the treatment of **chronic urticaria.**

SUCROSUM

(Sucros.). $C_{12}H_{22}O_{11}$

Syn.—Saccharum Purificatum ; Refined Sugar ; Cane Sugar ; *Misri, Chini,* Beng.

Source.—Sucrose is obtained from the juice of the *sugar-cane*, or of the *sugar-beet.*

Characters.—Colourless crystals or crystalline masses or a white powder ; no odour ; taste, sweet. Readily *soluble* in 0.5 part of water.

Enters into.—Preparation of all syrups.

ACTION AND USES

Sugar is a food, and tends to produce fat and helps to maintain body-heat. It is a demulcent and preservative, and in the form of syrup it is added to various pharmaceutical preparations to cover the disagreeable taste of drugs.

Part of it is decomposed in the gut with the formation of acid and gas. It delays digestion and favours development of hyperacidity. Sugar is a valuable **diuretic** and removes oedema. In the blood it produces a transitory hyperaemia by osmosis, and like salts and urea hinders absorption of water from the tubules.

100 mils ($3\frac{1}{2}$ ozs.) of 50 p.c. solution of sucrose has been used intravenously to **reduce intracranial pressure** in head injury without producing a subsequent rise or other untoward effects as are observed after injection of sodium chloride and dextrose.

LACTOSUM

(Lactos.). Lactose. $C_{12}H_{22}O_{11},H_2O$

Syn.—Saccharum Lactis ; Milk Sugar.—Lactose may be obtained from the whey of milk.

Characters.—A white, crystalline powder ; odourless ; taste, slightly sweet. *Solubility.*—1 in 7 parts of cold, more in hot water ; almost insoluble in alcohol (90 p. c.).

PHARMACOLOGY AND THERAPEUTICS

Internally.—Lactose is a valuable nutrient, and being less sweet than cane sugar is largely used. It greatly in-

creases the flow of urine and is therefore given in cardiac and renal dropsies. It is largely used in humanising cow's milk for infants and because it does not ferment in the stomach it is the best sweetening agent in infantile dyspepsia and irritable conditions of the stomach. It is considered to be a physiological accelerator of labour pains and for this purpose doses of 5½ to 7 drs. may be given dissolved in half a pint of milk.

On account of its hardness lactose is used to facilitate the minute subdivision of other drugs, or to dilute potent substances and bring them up to a uniform standard.

DEXTROSUM

(Dextros.). Dextrose. $C_6H_{12}O_6$

Syn.—Anhydrous Dextrose; Grape Sugar.

Source and Characters.—May be prepared from starch by hydrolysis. In white, crystalline or granular powder; odourless; taste, sweet. *Soluble* in less than 1 part of water, in 50 parts of cold alcohol (90 p.c.), in 5 parts of boiling alcohol (90 p.c.).

OFFICIAL PREPARATIONS

1. **Injectio Dextrosi.**—When no strength is stated, a solution containing 5.? p.c. w/v shall be dispensed.
2. **Injectio Sodii Citratis cum Dextroso.**—See page 79.

DEXTROSUM HYDRATUM. (Dextros. Hyd.). **Syn.**—Medicinal Glucose; Purified Glucose.—Dextrose Monohydrate may be prepared from starch by hydrolysis.

Characters.—Colourless crystals, or a white or cream-coloured, crystalline or granular powder; odourless; taste, sweet. *Soluble* in less than 1 part of water; in 50 parts of alcohol (90 p.c.).

GLUCOSUM LIQUIDUM. (Glucos. Liq.). **Syn.**—Corn Syrup.

Source.—Liquid Glucose is obtained by the hydrolysis of starch, and consists of a mixture of dextrose, maltose, dextrin and water.

Characters.—A colourless, or almost colourless, very viscous syrup; odourless; taste, sweet. Freely mixes with water forming a clear solution; *partly soluble* in alcohol (90 p.c.).

Enters into.—Ferr. Carb. Sacch.

OFFICIAL PREPARATION

1. **Syrupus Glucosi Liquidi.** *Syn.—Syrup of Glucose.*—33.3 p.c.

PHARMACOLOGY AND THERAPEUTICS

Dextrose is rapidly absorbed when administered by the mouth. Given by the rectum or subcutaneously it does not raise the sugar in the blood so easily. A definite rise of blood-sugar occurs when given as rectal injection with saline. It undergoes oxidation in the body rapidly, but this depends upon the availability of insulin, and in the absence or deficiency of insulin it cannot be utilised.

To understand why dextrose has been found useful in various diseased conditions it is necessary that the student should recognise the following physiological functions which it performs in the body: (1) it is the natural sugar of the body and all nutritious carbohydrates are converted into it before absorption; (2) it yields energy to the body;

(3) it is essential for proper combustion of fat, and its deficiency causes incomplete combustion with formation of various fatty acids and reduction of alkali reserve with a tendency to formation of so-called acidosis; (4) it is stored as glycogen in the liver which is necessary for its proper function.

Given by the mouth it is of great value in nervousness and subnormal health in infancy supposed to be due to shortage of sugar, in asthmatic attacks of children, and in malnutrition. Dextrose is used as a preliminary to volatile anaesthesia to replenish the carbohydrate reserve and to avoid acidosis and delayed chloroform poisoning (*see* page 157). It is given intravenously to combat severe toxaemias, as for instance in pernicious vomiting of pregnancy, uraemia, eclampsia, etc. A 5 p.c. solution is approximately isotonic and may be used intravenously alone or with normal saline solution to increase the volume of circulating blood in the treatment of **shock** following severe surgical operations, **collapse of cholera, dehydration,** and as a **circulatory stimulant** in acute infectious fevers. It is more valuable than the ordinary injection of normal saline solution. In **cardiac failure** it may with advantage be combined with strophanthin. When given with insulin it improves the glycogen reserve of the heart muscle.

When dehydration is due to salt depletion, administration of intravenous dextrose increases excretion of fluid by the kidneys which carries with it enough additional salt to provoke salt depletion shock.

Dextrose exerts a special action on the liver to which it acts as a food. It is essential in the process of glycuronation and the liver deprived of glycogen becomes less resistant to toxic agent. It is therefore used to protect the liver from damage in poisoning by cinchophen, chloroform, carbon tetrachloride, arsphenamine, phosphorus and heavy metals. For the same reason it is of great value when given *before* a prolonged surgical operation in persons whose liver is affected by disease or is likely to be damaged.

It is a valuable article of diet in prolonged fever with tissue destruction, *e.g.* enteric fever. It is easily absorbed from the rectum, better than any other food, and is therefore largely used in the treatment of **gastric ulcer**, the patients being given 3 to 4 pints daily of saline sugar solutions thus giving the ulcers every chance of healing. It also prevents hypoglycaemia which may follow an overdose of insulin in the treatment of diabetes. Similarly when given with insulin it is valuable in **ketosis** or **coma of diabetes.**

Dextrose in concentrated solution and in sufficient amount to exceed the renal threshold, acts as a **diuretic** by

osmosis. The usual dose is 50 mils of a 50 p.c. solution *intravenously*. When given by the mouth much of it is stored as glycogen in the liver and will not produce sufficient concentration in the kidney to act as a diuretic.

Intravenous injection of hypertonic dextrose (25 p.c. is strongly hypertonic) causes a temporary reduction in the fluid pressure in the tissues by the withdrawal of water, and is used in arterial hypertension, and to **reduce intracranial pressure** in meningitis, fracture of the skull, etc. The solution should be freshly prepared and kept slightly above the body temperature and the injection made very slowly. After a short interval the pressure rises again much above normal, due to a reactionary rise in the intracranial pressure which constitutes a serious drawback to this method of treatment. This has been ascribed to an increase in the quantity of hydrolysable carbohydrate in the cerebro-spinal fluid which alters its composition and **consequently its osmotic pressure.**

5 to 10 mils (75 to 150 ms.) of a mixture containing equal parts of dextrose 25 p.c. and sodium chloride solution 15 p.c. used at one injection is considered as the best treatment for **varicose veins.** The solution should be left in contact with the endothelium for at least 5 minutes with a vein occluder, and subsequently strapped with a gauze **pad to compress the vein.**

For oral administration liquid glucose may be used; but should not be used for injection. It is largely used in **pharmacy as an excipient for pills.**

Caution.—Large quantities may give rise to nausea, restlessness, tremors, convulsion and coma. The intravenous injection should be given very slowly, 4 mils (60 ms.) per minute, specially when concentrated solution is used. When a large amount is rapidly thrown into the blood it may cause over-stimulation of insulin producing symptoms of hypoglycaemia, or may cause acute dilatation of the heart. It is better to use insulin to prevent this and also to metabolise the large amount of sugar thus introduced. Intravenous injection should be avoided when dehydration is due to salt depletion (see page 89). For intramuscular use the solution should not be stronger than 12.5 p.c. and not more than 50 mils (12½ drs.) **should be given at a time.**

LAEVULOSUM. (Laevulos.). Laevulose. $C_6H_{12}O_6$. Syn.—*Fructose.*

Source.—Prepared from invert sugar, or from honey. Contains laevulose together with small quantities of dextrose and water.

Characters.—A white or cream coloured, hygroscopic, crystalline powder. Odourless; taste, sweet. Freely *soluble* in water.

ACTION AND USES

Laevulose is more sweet than cane sugar and is more easily assimilated. Like other laevorotatory carbohydrates it is utilised by diabetics and has therefore been used without increasing the excretion of sugar. It is

largely used in wasting diseases, specially tuberculosis an scrofula, when as much as several ounces are taken dail

In normal healthy persons all ordinary sugars, gluco etc., when administered raise the concentration of th blood-sugar, but not laevulose, if the liver is healthy ; fo part is oxidised and part is stored as glycogen. If th glycogenic function of the liver is impaired by disease th rate of utilisation fails to keep pace with the rate of ab sorption and an abnormally large amount of laevulos passes through the liver into the general circulation. Th forms the basis of laevulose tolerance test of hepatic func tion. After a fast of 12 hours a dose of 50 grms. (1½ ozs. is administered dissolved in 4 to 5 ozs. of water, and th blood-sugar is estimated every half hour for two hours A rise of 0.03 p.c. above the fasting level indicates hepati disorder.

GELATINUM. (Gelat.).—Gelatin is the protein which is ob tained by extraction from collagenous material.

Characters.—Colourless, or pale yellowish, translucent sheets, shreds, powd or granules ; odour and taste, slight. *Insoluble* in cold water, but swells an softens when immersed in it, gradually absorbing from five to ten times its ow weight of water ; soluble in hot water, forming a jelly on cooling ; insoluble i alcohol (90 p. c.), in solvent ether, and in chloroform.

Enters into.—Suppositoria Glycerini.

Official Preparation

1. **Gelatinum Zinci.** *Syn.—Unna's Paste.*—Zinc Oxide 15 p. c., Gelatin 15 p. c

Uses

Gelatin is used as a basis for several pharmaceutical prepara tions such as pastes, suppositories, pessaries, bougies, discs, gelati capsules, and as a coating for pills. It is largely employed in dietar for making jellies, etc.

It is a powerful protein sparer but since it does not contai tyrosine and tryptophane it cannot supply the whole protein nee of the body. But when given with other foods, specially with mil it forms a valuable food.

For its colloidal value gelatin is sometimes used with saline in fusions in the treatment of collapse and shock ; but as has bee pointed out elsewhere (*see* page 88) it may cause dangerou symptoms of anaphylactoid reaction producing respiratory distres and cardiac dilatation. Its use has been replaced by blood plasm which is now available.

INJECTIO PROTEINI HYDROLYSATI, I. P. L. Syn.—Pepton Glucose Solution.—Injection of Protein Hydrolysate is a mixture o the products of hydrolysis of a biologically complete protein and con sists essentially of amino-acids with added glucose and sodiu chloride. Contains glucose 5 p.c., sodium chloride 0.9 p.c. and tota nitrogen 0.75 to 0.80 p.c.

Characters.—A clear brownish-red liquid ; odour, meaty ; taste, characteristi Slightly acidic to solution of litmus.

Dose.—7 to 15 ozs. or 200 to 400 mils by intravenous injection.

Action and Uses

Proteins form one of the chief proximate principles of food an although fats and carbohydrates supply heat and energy, they can not build up or repair tissue waste, since they do not contain an nitrogen. The value of proteins depends upon their amino-acid con

ents which are the end products of protein digestion in the alimentary canal. The amino-acids after absorption pass into the liver and thence to the systemic circulation and utilised for building up of tissues. Of the twenty-one or more amino-acids only ten are essential. Normally there is a large storage of amino-acids or protein in the liver, muscles and other tissues. These reservoirs may be depleted by (1) insufficient intake as in the under-nourished ; (2) faulty digestion or impaired absorption, as in persons suffering from diarrhoea or chronic intestinal trouble ; (3) impaired protein synthesis, as happens in diseases of the liver or infections ; (4) increased protein loss, as in ascites, haemorrhage, shock, nephrotic syndromes ; and (5) increased breakdown of body protein, as in persons having high basal metabolic rate, fevers, pregnancy, lactation, etc. Amino-acid therapy therefore is indicated in any of the above conditions. Administration of a suitable protein intravenously has yielded satisfactory results by supplying nitrogen in **hypoproteinaemia** not only by increasing plasma protein itself, but also by supplying all the essentials of protein metabolism, including haemoglobin formation.

Protein hydrolysate has been used in cases of starvation in a state of collapse with great benefit. In starvation the nitrogen requirement of the body is urgent and hydrolysed protein when administered intravenously will supply more nitrogen than when given by the mouth as then its absorption is slow and uncertain, and since the amino-acids reach the liver first, which is damaged, no synthesis takes place. The marked and rapid improvement following its use show that the amino-acids and peptides are being readily utilised. Glucose helps to repair the liver damage and increases its functional activity, and by preventing protein breakdown helps in the synthesis of tissue protein from the amino-acids.

The injections are given with the help of Haye's pattern transfusion set very slowly; 200 mils taking about an hour, and the effect lasts for 24 hours. They are repeated daily for three or four days ; each injection providing 100 to 200 calories.

Before giving the injections it is advisable to examine the urine for albumin and casts, but this is not absolutely essential. Even when no urine is available, or when the patient is in an extreme state of collapse, or the urine shows traces of albumin, it may be safely administered. But when extensive damage to the kidney or liver is suspected, it is preferable to give dextrose-saline first and when improvement is noticed then protein hydrolysate should be given.

It is a rich source of nutriment and has been used in **gastric and doudenal ulcer**, in doses of 300 to 400 grms. daily in 8 to 9 divided doses by the mouth, when it ensures adequate nitrogen balance with less burden to the gastro-intestinal tract. It has also been used in severe **haemorrhage, hepatic cirrhosis, acute and chronic hapatitis and food idiosyncrasies.**

It may be used orally or parenterally. Because of the taste, which is objectionable in some preparations, the oral use is limited. This can be avoided by mixing the preparation with milk, malted milk or fruit juice. A mixture of vitamins, such as aneurine 10 mg. should be added to the daily intravenous solution to supply the valuable nutritional elements in a readily assimilable form.

Caution.—Fever, nausea and vomiting may occur if the injections are given rapidly.

Amigen, N. N. R. (Not official).—It is a hydrolysate of casein. Contains all essential amino-acids and some di- and tri-peptides. To be administered orally. Dosage is determined by the weight and requirements of the patient. 1 grm. protein is equivalent to 1.3 grm. of Amigen.

Methionine.—It is *α*-amino- *γ*-methylthiolbutyric acid. Occurs as white, lustrous platelets or crystalline powder, with a faint characteristic odour. It is one of the sulphur-containing amino acids of the food which pass through the liver and utilised for tissue repair and more specifically for the formation of insulin, glutathione, keratin of skin, etc. In the body it yields a methyl group which is utilised in the synthesis of cystine and choline. Methionine and choline mobilise or prevent deposition of excess of fat in the liver, *i.e.* they are "lipotropic" (*see* page 237). It has been used for the prevention and treatment of injury to the liver which may occur in carbon tetrachloride and chloroform anaesthesia. These are treated with high protein and low fat diet, together with 0.5 to 2 grm. of methionine daily. It has also been recommended in **cirrhosis of the liver** and **infectious hepatitis**. Its value in infectious hepatitis is doubtful.

Dose.—0.5 to 2 grm. up to 5 grm. in severe cases by the mouth daily.

Ovolecithin, B. P. C. Syn.—Egg Lecithin.—It is a normal constituent of brain substance and is obtained from yolk of egg. It is yellowish, wax-like substance, insoluble in water.

Dose.—By mouth, 3 to 8 grs. or 0.2 to 0.5 grm.

Action and Uses.—Little if any lecithin is absorbed as such, but it is broken up by the pancreatic juice into glycerophosphoric acid, fatty acids, and choline. It is used chiefly for its supposed action in **improving the nutrition** of the nervous system. It is also stated to increase the number of red blood-corpuscles and to raise their haemoglobin content. It increases body-weight and improves general nutrition.

GROUP XIX

DRUGS HAVING EFFECT IN URIC ACID DIATHESIS

Colchicum, Cinchophen

COLCHICI CORMUS

Colchicum Corm. (Colch. Corm.)

Source.—It is the corm of *Colchicum autumnale*, collected in early summer, deprived of its coats, sliced and dried at a temperature not exceeding 65°C. The dried corm contains not less than 0.25 p.c. of colchicine.

Characters.—Slices, sub-reniform or ovate in outline, about 1 to 3 by 1 to 2 cm. and 2 to 5 mm. thick ; edges, yellowish-brown ; slices, firm and breaking readily with a short mealy fracture ; transverse surfaces, white and starchy and exhibiting numerous scattered fibro-vascular bundles, occasional subconical pieces from the apex and irregular pieces from the base of the corm, also sometimes in longitudinal slices. Odourless, taste, bitter and acrid.

Composition.—(1) *Colchicine*, an active alkaloid. (2) *Starch*, gum, sugar, tannin, etc.

Incompatibles.—Astringents, tincture of iodine and guaiacum.

Colchici Cormi Pulvis. (Colch. Corm. Pulv.).—Powdered Colchicum Corm is light grey.

Official Preparation

1. **Extractum Colchici Siccum.**—Contains 1 p. c. colchicine or 1/200 gr. in 1/2 gr. **B. P. Dose.—1/6 to 1/2 gr. or 10 to 30 mg.**

COLCHICI SEMEN. (Colch. Sem.). Colchicum Seed is the dried ripe seeds of *Colchicum autumnale*.

Characters.—2 to 3 mm. in diameter, subglobular, slightly pointed, rough, reddish-brown, hard, tough, minutely pitted. Endosperm, oily. Taste, bitter. No odour.

Composition.—(1) *Colchicine* 0.3 to 0.6 p. c. (2) A fixed oil.

Colchici Semina Pulvis. (Colch. Sem. Pulv.).—Powdered colchicum Seed is brown.

Official Preparations

(1) **Extractum Colchici Liquidum.** *Syn.—Fluid Extract of Colchicum.*—Contains [illegible] p. c. w/v of colchicine.

(2) **Tinctura Colchici.—Contains 0.03 p. c. w/v of colchicine,** or 1/200 gr. in 15 ms. **B. P. Dose.—5 to 15 ms. or 0.3 to 1 mil.**

COLCHICINA. (Colchicin.).—Colchicine is the alkaloid obtained from the corm and seeds of *Colchicum autumnale.*

Characters. Pale yellow crystals, amorphous scales, or powder ; odourless ; taste bitter ; darkens on exposure to light. Readily *soluble* in water ; soluble at 15.5° in about 160 parts of solvent ether, freely in alcohol (95 p. c.) and in chloroform.

B. P. Dose.—1/120 to 1/60 gr. or 0.5 to 1 mg. Total Dose :—**1/30 to 1/8 gr. or 2 to 8 mg.**

Pharmacology

Internally. **Gastro-intestinal tract.**—In moderate doses colchicum causes purging, vomiting and abdominal pain. In large doses it is a powerful gastro-intestinal irritant. These symptoms appear several hours after administration even if the dose is large. This is probably due to the conversion into oxydicolchicine. According to Dixon colchicine acts on the intestine in the same way as pilocarpine and is antagonised by atropine. This however does not explain the whole action, *e.g.* acute inflammatory reactions, which are really due to the irritant action of the drug on the mucous membrane, or being due to capillary vaso-dilatation produced by the drug either directly or through excretion.

Circulation and respiration.—It depresses the circulation, lowers the blood pressure and slows the respiration. The pulse becomes feeble, soft and rapid. These effects are not due to any direct action on the circulatory organs. Death takes place from failure of respiratory centre.

Kidneys.—Its action on the kidneys is uncertain. In some there is anuria, in others there is an increase of urine. The urinary constituents are not affected.

Acute toxic action.—The chief symptoms are those of gastro-intestinal irritation in a grave form. Violent burning in the throat, oesophagus and stomach ; intense thirst ; severe colic with vomiting and purging ; the stools being first serous, then slimy and finally bloody ; great prostration, rapid, feeble and thready pulse ; cold skin bedewed with sweat ; slow and laboured respiration and lastly death during collapse from respiratory paralysis ; consciousness not being lost.

Treatment.—Emetics, followed by demulcent drinks, as white of egg freely diluted with water. Tannic acid is a chemical antidote. Stimulants, tea, and coffee ; morphine hypodermically.

Chronic toxic action.—Small medicinal doses long continued, bring about furred tongue, disagreeable taste, loss of appetite, thirst, epigastric pain, flatulence and diarrhoea.

Therapeutics

Internally.—Colchicum is a specific in acute gout. The severest pain and inflammation are removed in a few

hours after 15 to 20 ms. of the tincture. It acts bette when combined with salicylate of soda and bicarbonate o soda each 20 grs. How it acts in this disease is not known It neither lowers the serum level of uric acid nor increase its excretion. Besides its specific property in gout, colchi cum is useful in many other complaints of gouty people such as dyspepsia, headache, hepatic congestion, neuralgia etc.

Caution.—It should be avoided or given with caution to the weak, the infirm, and those who suffer from cardiac weakness, chronic diarrhoea, chronic dysentery or colic.

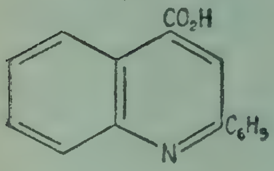
Prescribing hints.—Colchicum may be administered in *acute gout* either in full doses say 15 to 20 ms. of the tincture repeated every 2, 3 or 4 hours, or in repeated small doses, say 10 ms. of the tincture, with salicylate of soda and an alkali at first every 2 to 3 hours for the first twelve hours and then three or four times daily. Colchicine is administered in the form of pills or capsules in doses of 1/120 gr. (0.5 mg.), repeated every 2 or 3 hours till relief of pain or vomiting or diarrhoea sets in. The first dose may be 1/60 gr. (1 mg.). Provided the patient is kept in bed, the pain is relieved in 24 to 72 hours. The total quantity required to give relief is between 1/16 to 1/8 gr. (4 to 8 mg.).

CINCHOPHENUM

(Cinchophen.). Cinchophen

Syn.—Quinophan ; Atophan ; Agotan.

Source.—It is 2-phenylquinoline-4-carboxylic acid. Prepared by the interaction of pyruvic acid and benzylideneaniline. Contains not less than 99 p.c. $C_{16}H_{11}O_2N$.



Characters.—White, or yellowish, powder or crystals ; almost odourless ; taste, slightly bitter. *Insoluble* in water, soluble in about 120 parts of alcohol (95 p. c.), in about 100 parts of solvent ether, and in solutions of alkali hydroxides, carbonates and bicarbonates.

B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

Neocinchophenum, U. S. P.—Ethyl ester of 6-methyl-2-phenylquinolin-4-carboxylic acid. White to pale-yellow, crystalline powder Odourless and tasteless. Nearly insoluble in water. Soluble in hot alcohol and very soluble in ether and in chloroform.

Dose, U. S. P.—5 grs. or 0.3 grm.

Pharmacology and Therapeutics

Cinchophen resembles the salicylates in its action and it is an *antipyretic*, *analgesic* and *antirheumatic*. It reduces temperature by causing vaso-dilatation and diaphoresis.

In therapeutic doses, even on a purine free diet, it increases the **elimination of urates and uric acid** and causes a fall in the uric acid content of the blood. It does not interfere with the uric acid formation excepting eliminating it in increasing amount. This effect continues as long as the drug is used. It acts either by increasing the permeability of the kidneys to uric acid or by hindering the normal reabsorption of urates by the tubules. To prevent

precipitation of urates, the urine should be kept alkaline by the administration of bicarbonate, acetate or citrate of potassium or sodium.

It is eliminated within 3 to 6 hours after ingestion.

Cinchophen is used in **gout** and its effects are more marked in acute attacks relieving both pain and swelling rapidly. The usual dose is 7½ grs. three or four times a day. It is specially useful in chronic cases where the uric acid level in the blood is persistently high. These patients derive great benefit with periodical course of cinchophen in 7½ gr. and bicarbonate of soda 30 grs. three times a day for 3 to 4 days at a time with rest for one week. Bicarbonate of soda diminishes the irritating effect of the drug in the stomach. It is also used in **acute rheumatic fever** in doses of 10 grs. three or four times a day. Such large doses do not cause nausea or irritation of the kidneys and are better tolerated when given with alkalies.

For its analgesic effect it is used in sciatica, headaches and neuralgias.

As a rule no untoward effects are noticed even when used in large doses. But attention has been drawn to cases of poisoning following its use. In many cases the symptoms are those of cinchonism with cutaneous rashes, gastro-intestinal and hepatic disorders. Occasionally vertigo, jaundice, digestive trouble, anorexia, fever and urticarial eruptions may appear. Cases of acute yellow atrophy of the liver have been recorded due either to individual susceptibility or uninterrupted use for prolonged periods. Albuminuria or any kind of nephritis should be regarded as contra-indication. Disturbed kidney function possibly retards excretion of the drug, but impairment of the liver function renders the patient more susceptible to the drug. If there is nausea or impairment of appetite its use should be withheld.

It should be taken *after meals* followed by a draught of water. Because of the danger of accumulation, the treatment should not be continuous, but should have periods of rest.

Neocinchophen is tasteless and does not cause gastric irritation. It is considered much safer to the liver than cinchophen. It is however less analgesic.

Toxic symptoms.—Severe jaundice with tender enlarged liver, definite haemorrhagic rash, bilirubin and albumin in the urine, with pale stool without any bile were observed in a man who had 118 grms. in 41 days for chronic rheumatism. Coagulation time of the blood was increased (7 minutes), bleeding time was normal. During the illness nitrogen excretion was high (15 to 18 grms. daily) showing breakdown of tissue protein. Death from subacute yellow atrophy of the liver after 37½ grs. in five days have been reported by Fraser. Toxic symptoms have been observed after doses ranging from 54 grs. in five weeks to 7,200 grs. in four months.

Treatment.—Stoppage of the drug and administration of dextrose 60 grms. (2 ozs.) with 20 units of insulin twice a day followed by duodenal lavage and administration of magnesium sulphate.

GROUP XX

DRUGS ACTING ON METABOLISIM

Metabolism is the sum total of the chemical exchanges taking place in the tissues through the medium of the blood. These exchanges represent two phases, *viz.*, *anabolic* and *katabolic.* The changes by which the different food materials are utilised in the building of the body represent the anabolic or constructive phase ; whereas the breaking down process by which the waste products are produced with liberation of heat and energy represent the katabolic phase. The products of metabolism are CO_2, urea, water, sulphate, etc., and these are excreted by the lungs, with urine, faeces and sweat. The oxygen taken up by the lungs plays a most important part and the physiological oxidation of the body cannot be separated from the general metabolic phenomena.

Metabolism therefore embraces all changes taking place in the body, and the most important factors concerned in the regulation of metabolism are food, exercise, light and air. Normally the anabolic and katabolic processes are more or less balanced ; the income in food being balanced by the expenditure of carbon, nitrogen and water in the urine, stool, sweat and respiration.

The term *basal metabolism* is used to denote the amount of potential energy or heat required to maintain the heat of the body, activity of the heart, respiratory movements, etc., when in complete rest. It is the smallest energy output compatible with health. Basal metabolism is in proportion to the surface of the skin, and since a tall person has a larger skin area, he requires more heat and therefore more food to keep the temperature normal.

Since the body is undergoing constant changes, the elements which go to build and maintain the body must perforce be subject to similar changes. Food is therefore necessary for growth and to replace the wear and tear of the body. The proteins contribute to the formation and repair of tissues, regulate the absorption and utilisation of oxygen and play an important part in the chemistry of nutrition. They are characterised by the presence of nitrogen. If the income of nitrogen received from the protein food is equal to the amount of nitrogen eliminated with the different excreta, the body is then said to be in nitrogen equilibrium. If less is eliminated, it implies that the body is storing protein, whereas if more is excreted then the body is losing protein. During the growing period and convalescence, less nitrogen is eliminated to enable the body to build up tissue. Under normal condi-

tions our diet is so regulated that the nitrogen equilibrium is maintained at a constant level. Proteins stimulate metabolism and the specific dynamic action is the result of deamination of the amino-acid, glycin, etc.

Carbohydrates and fats play the same role in the body, being sources of heat and energy. Fat however may be stored up in the tissue as part of body fat, or may be synthesised with other substances to form more complex constituents of the body, *viz.*, lipids. Carbohydrate is oxidised in the body to supply the necessary heat and is stored up as glycogen in the liver and muscles to be doled out as sugar according to the requirements of the body for use in tissue metabolism. This important function may be disorganised through various causes, *viz.*, injury to the central nervous system, and over secretion of the adrenals or hypophysis, and is regulated by the internal secretion of the pancreas.

The role of vitamins in the general metabolism is now widely recognised and diseases like rickets, beri-beri, scurvy and pellagra are regarded as the result of metabolic disturbances caused by deficiency of certain vitamins in the food.

Inorganic metabolism.—Since most of the therapeutic measures depend for their action on the alteration they produce in the inorganic constituents of the body, a knowledge of the metabolism of the inorganic salts is a great help to the pharmacologist. Mineral salts form about one-twentyfifth part of the whole body. The chief mineral elements are calcium, sodium, potassium, magnesium, iron, manganese, zinc, copper, lithium and barium ; phosphorus, sulphur, chlorine, silicon, fluorine, etc. Of these calcium, sodium, potassium, manganese, iron and copper are the most important and are the alkali forming elements ; while phosphorus, sulphur and chlorine are the acid forming ones. These salts form an essential part in the composition of living matter and maintain a normal composition and osmotic pressure in fluids and tissues of the body and play an important part in the regulation of the acid-alkali balance. Sodium chloride occurs in all the tissues and fluids of the body. Since every cell contains phosphorus, it is essential for the multiplication of cells and growth of the body. The phosphates of sodium and potassium regulate the reaction of body fluids and tissues, control the osmotic pressure and interchange of fluids. Calcium phosphate is essential for the development of bones, and calcium itself performs many important functions already discussed (*see* page 98). Calcium metabolism is intimately related to vitamin D, parathyroid and thyroid, also on the reaction of the blood ; acidosis helps retention of ionised calcium, while alkalosis decreases the amount of diffusible calcium

and produces tetany. Iron is an important element of haemoglobin. It is also present in minute quantities in the muscles and other tissues where it helps the oxidation and catalysis of enzymes. Iodine is stored up as thyroxine in the thyroid gland and deficiency of iodine results in goitre.

Within recent years the effects of light and air on metabolism have received much attention owing to the admirable work of Sir Leonard Hill. He has shown that under cool open air condition the tone of the body is much increased, and the growth of infants becomes more rapid in the cool months. Exposure of the body to the cool atmosphere has a stimulating effect on the general metabolism, whereas heat has a depressing effect with a lower basal metabolism. A sufficiency of sunlight with cool, dry and moving air is conducive to health and gives a feeling of well-being. Light and air exert a much more important effect on the body metabolism. The ultra-violet rays of the sunlight are absorbed by the skin and form vitamin D so important for the formation of bony skeleton and prevention of rickets. Similarly exercise by throwing more work on the muscle increases protoplasmic activity which implies supply of more nutrient material and oxygen.

THYROIDEUM

Thyroid. (Thyroid.)

Syn.—Thyroideum Siccum ; Thyroid Extract ; Desiccated Thyroid Gland.

Source.—Prepared from the thyroid gland of oxen, sheep, or pigs. Contains 0.1 p.c. of iodine in combination as thyroxine.

Characters.—A cream-coloured amorphous powder. Odour and taste, faint and meat-like.

Storage.—Thyroid should be kept in well-closed container, and stored in a cool place.

B. P. Dose.—1/2 to 2 grs. or 30 to 120 mg.

Official Preparation

1. **Tabellae Thyroidei.—B. P. Dose.—1/2 to 2 grs. or 30 to 120 mg.** N. B. When the quantity in each tablet is not stated, 1/2 gr. tablets shall be supplied.

Pharmacology

The hormone thyroxine is an amino-acid and is a derivative of tyrosine similar to adrenaline. It forms part of the protein *thyroglobulin* stored in the colloid of the thyroid follicles. While the absorption of thyroxine from the stomach is irregular, thyroglobulin or crude thyroid gland is readily absorbed. When either thyroxine or thyroid extract is administered to normal persons no obvious effects are observed unless it is pushed to elicit toxic symptoms. The effects observed are quickening of the pulse, vomiting and diarrhoea, increased metabolism, particularly an increase of nitrogenous metabolism, loss of weight and emaciation. A single dose has very little effect, but small

repeated doses produce toxic symptoms. In fact a single large dose even when administered intravenously does not produce any effect for 24 to 36 hours. Full effects are observed in three to four days. Continued use tends to produce cumulative effects.

Anterior pituitary through the thyrotrophic hormone stimulates the thyroid and causes hyperplasia of the cells and discharge of colloid containing thyroxine causing symptoms of hyperthyroidism ; and its loss or insufficiency is followed by atrophy of the gland. Thyroid and adrenaline work together and the activity of the thyroid depends upon adrenaline and conversely thyroid secretion sensitises tissues to the action of adrenaline. All the effects of hyperthyroidism are those of sympathetic stimulation and in the absence of its hormone all response to sympathetic stimulation is diminished. (*See* page 229).

Internally. **Circulation.**—Given by the mouth for a prolonged period, thyroid causes increase in the pulse-rate, palpitation and weakness of the heart-beat. Sometimes no acceleration is observed even after its use for a long time. This is possibly due either to deterioration or to absence of thyroxine from the dried gland. The cause of acceleration is not clearly understood, and may be due to stimulation of the sympathetic or to direct action on the heart. It has been suggested that it blocks the vagal impulse thus producing tachycardia. Given by the mouth it has no effect in reducing the blood pressure.

Metabolism.—Thyroid increases metabolism of the proteins, fat and carbohydrates even in normal animals, although it is more marked when it is low as in thyroid deficiency. The excretion of nitrogen and carbonic acid, and the consumption of oxygen, are increased, so that an excess of urea, uric acid and xanthin bases is eliminated through the kidneys and more carbonic acid by the lungs. In fact more nitrogen is excreted than is taken by the food, which implies that the excess is due to destruction of tissue protein, and since the glycogenic function of the liver is disorganised, the use of carbohydrate or fat does not check the protein destruction. The carbohydrates disappear from the liver and the fats from the fat depots and the blood sugar rises and may appear in the urine. It also influences the calcium metabolism and helps removal of calcium (together with phosphorus) from the bones thus making them rarefied (osteoporosis), but there is no increase of serum calcium as happens with parathormone, and there is increased excretion in the urine and faeces. As a result of all these effects the body temperature rises, and the weight falls which is greater than can be accounted for by the loss of tissue protein. Cushny suggests that the most important factor in the reduction of weight is

diuresis, which helps to eliminate a large amount of fluid not only in subjects of myxoedema but also in persons suffering from obesity.

The basal metabolism is increased about 2 to 3 p.c. by 1 mg. of thyroxine in adults weighing 150 pounds, due to increase of fat and carbohydrate metabolism. In myxoedemic patients 10 mg. may produce an increase of 30 p. c. The results are the same whether thyroxine is given by the mouth or intravenously. If it is continued in large doses, symptoms of hyperthyroidism become marked by the 5th or 6th day.

The normal human thyroid contains about 10 to 15 mg. of iodine, but this depends upon the quantity of iodine taken with food. When iodides are given this iodine is doubled. The gland is concerned in the development and maintenance of the normal functions of the body, and this it does by virtue of its internal secretion, which can only be formed when there is a certain amount of iodine in the food. According to Bircher thyroid promotes the growth of bone in normal animals and for this reason has been used to promote union of bones in delayed healing of fractures.

Kidneys.—Thyroid is a powerful **diuretic.** The increased excretion of urea is partly responsible for the effect. It has been suggested that hyperthyroidism renders the antidiuretic hormone less effective. It is possible that the passage of a large amount of water and sodium chloride to the circulation produces hydraemia of the blood with consequent diuresis.

Excretion.—It is chiefly excreted by the kidneys, and when continued long may cause gastro-intestinal disturbances and diarrhoea.

Acute Thyroidism.—The symptoms produced by an overdose are as follows :—Rapid pulse, fever, headache, tendency to syncope, sickness, diarrhoea, restlessness, wandering pains, pruritus, and rarely delirium.

Chronic Thyroidism.—The symptoms are :—Loss of weight. muscular weakness and paresis, falling out of the hair, protrusion of the eyeballs, dilatation of the pupils with widening of the palpebral fissure, and finally death from malnutrition and asthenia. It will be noted that these symptoms closely resemble those of exophthalmic goitre.

THERAPEUTICS

The chief use of thyroid is in the treatment of **myxoedema** which is a disease due to the atrophy of the thyroid gland and is characterised by slow pulse, dry skin, loose hair, sluggish bowel and dull brain with low metabolism and consequently diminished oxygen consumption. In six weeks all symptoms will probably have disappeared, but to prevent recurrence the patient must take it twice a week for the rest of his life. In the same way it is invaluable

in **cretinism**, which is a form of idiocy associated with dwarf growth, due to congenital absence of the thyroid. Under this treatment, however, the bones of cretins have a strange tendency to bend. Thyroid has also proved of benefit in congenital imbecility, the insanity of the menopause and in menopausal headache, specially when associated with subnormal metabolic rate.

Paradoxical as it may appear thyroid is useful in goitre. In this condition the enlargement of the gland does not mean increased secretion, on the other hand the gland hypertrophies to compensate for the deficiency of the thyroxine. But it is useless in exophthalmic goitre. As thyroid hormone stimulates metabolism, it has been used in diverse conditions. For instance, remarkable results may be obtained in certain diseases of the skin, specially psoriasis, pityriasis rubra, ichthyosis, eczema, lupus, etc., whilst it sometimes causes a luxuriant growth of hair in alopecia. Administered with calcium it is of value in chilblains.

In constitutional **obesity** thyroid treatment has been found to be of value, but may do harm if used without proper precaution. It sometimes reduces the weight to a great extent, but the effect should be regarded as the toxic effect and is often followed by symptoms of hyperthyroidism. Small doses of thyroid form a valuable remedy in obstinate constipation so often present in slight forms of hypothyroidism.

Thyroid deficiency is to a large extent responsible for a number of complaints and infections, and its administration has been advocated in acute and chronic arthritis, phlegmasia alba dolens, *Bact. coli* infection and chronic gout.

As a diuretic it is said to be valuable in reducing oedema of Bright's disease.

Cheron used it as a galactogogue, and in threatened abortion. Different observers have reported benefit from its use in infantile wasting, ununited fracture, and in assisting the development of backward children.

It is worthy of trial in children who fail to grow, in nocturnal enuresis, night terrors, and in those who suffer from relaxation of the ligaments causing knock knee, painful heel, flat foot or lordosis.

Prescribing hints.—Thyroid is best administered in the form of powder or as tablets. It is not as a rule a dangerous remedy, but when it is continued for a prolonged period it should be used with care, specially if the heart is affected. It is now realised that large doses are not required. A total daily dose of 6 grs. of the extract of fresh gland seldom needs to be exceeded, and it is wise to start with 1/2 gr. doses three times a day. It should be noted that the extract of the desiccated gland is five times as strong as the fresh gland.

Contra-indications.—Hypersecretion of the thyroid, and when there are toxic symptoms from hyperthyroidism. Sleeplessness, delirium, cerebral excitement and when the heart is rapid or irritable. In acute inflammatory condition of the skin and progressive loss of weight.

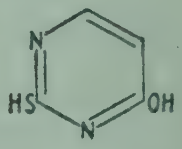
Antithyroid Drugs

Till recently only methods available for the treatment of hyperthyroidism were either removal of part of the thyroid gland or the administration of iodine which, however, produces only temporary benefit and generally used as a preliminary to operation.

In has been observed that a number of sulphur-containing compounds such as sulphonamide derivatives (sulphaguanidine was actually used for experimental purposes) and thiocyanates, when ingested for prolonged periods produced enlargement of the thyroid with signs of thyroid hypofunction, and caused reduction in the basal metabolic rate, impairment of growth and development. The same results were also obtained when phenylthiourea was used. It was further observed that simultaneous administration of thyroid or thyroxine prevented sulphaguanidine from causing thyroid enlargement. It was therefore concluded that sulphaguanidine reduces the rate of thyroxine formation. A large number of compounds were tried by Astwood and his co-workers with the result that thiouracil derivatives have been found to be least toxic and selected by Astwood for clinical trial.

Antithyroid drugs are: **Thiouracil, Methylthiouracil, Propylthiouracil** and **Iodine** (q.v.).

THIOURACILUM. (Thiouracil.).—Thiouracil is 2-mercapto-4-hydroxypyrimidine. Prepared by the condensation of ethyl formylacetate with thiourea.



H_4ON_2S

Characters.—A white or pale cream powder; odourless; taste, bitter. Very slightly *soluble* in water, in alcohol (90 p. c.), in solvent ether and in acids.

B. P. Dose.—1½ to 3 grs. or 0.1 to 0.2 grm.

Official Preparation

1. **Tabellae Thiouracili.**—**B. P. Dose.**—1½ to 3 grs. or 0.1 to 0.2 grm. N. B. If the quantity contained in the tablet is not stated, 1½ gr. tablet shall be supplied.

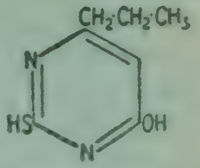
METHYLTHIOURACILUM. (Methylthiouracil.).—Methylthiouracil is 2-mercapto-4-hydroxy-6-methylpyrimidine.

Characters.—A white or pale cream powder; odourless; taste, bitter. Very slightly *soluble* in water, in alcohol (95 p.c.), in dilute mineral acids.
B. P. Dose.—3/4 to 3 grs. or 0.05 to 0.2 grm.

Official Preparation

1. **Tabellae Methylthiouracili.**—**B. P. Dose.**—3/4 to 3 grs. or 0.05 to 0.2 grm. N. B. If the quantity in each tablet is not stated, 1½ gr. tablet shall be supplied.

PROPYLTHIOURACILUM. .Syn.—Propacil.—Propylthiouracil is 4-hydroxy-2-mercapto-6-*n*-propylpyrimidine.



Characters.—White or pale cream powdery crystals; odourless; taste bitter. Very slightly soluble in water; sparingly soluble in alcohol (95 p.c.); slightly soluble in chloroform and in solvent ether.

B. P. Dose.—2/5 to 1½ gr. or 25 to 100 mg.

Official Preparation

1. **Tabellae Propylthiouracili.**—**B. P. Dose.**—2/5 to 1½ gr. or 25 to 100 mg.
N.B. When the quantity in a tablet is not stated, 2/5 gr. shall be supplied.

Action and Uses

Normally the formation and release of thyroxine depends upon thyrotrophic hormone of the anterior pituitary. Thyroxine regulates the metabolic rate of all the body tissues, which is reflected on the Basal Metabolic Rate. The treatment of hyperthyroidism aims at decreasing the synthesis of thyroxine to a normal level so that the patient will not be stimulated to produce thyroid hyperplasia. Because thiouracil or its derivative methylthiouracil causes inhibition of thyroid function by interfering with the formation of thyroxine from diiodotyrosine, these have been used in the treatment of hyperthyroid manifestations of toxic goitre, *i.e.* in thyrotoxicosis. They have been used with striking results in (a) primary thyrotoxicosis, (b) toxic adenoma, (c) thyrotoxicosis recurrent after partial thyroidectomy. After an initial period of about a week or so their administration brings on definite changes when continued for some weeks, as is evidenced by fall in pulse-rate and basal metabolic rate, rise of body weight and blood cholesterol, and amelioration of general features, e.g. sweating and nervousness. As the condition improves the dose should be reduced keeping the patient on the maintenance dose of 50 to 100 mg. (¾ to 1½ gr.) daily.

Absorption and clearance.—Thiouracil is rapidly absorbed from the gastro-intestinal canal and it is found in the blood within fifteen minutes after administration of 1½ to 3 grs. by the mouth. The peak of concentration is reached within 30 minutes. It is excreted by the kidneys unchanged only about 15 p.c. is possibly destroyed by the digestive juices. After absorption it is distributed in the different tissues of the body specially the pituitary, adrenal, thyroid, the gonads, and the cerebrospinal fluid and milk.

Propylthiouracil is rapidly absorbed when administered by the mouth. It is more prompt and the effects last longer. It is generally used to prepare the patient for thyroidectomy or in cases of thyrotoxicosis in place of thyroidectomy. Usual dose is 100 mg. (1½ gr.) daily divided into four equal portions and administered every six hours.

Produces distinct improvement within two days but may require ten days to several months for remission to occur.

Toxic effects.—Thiouracil is a double edged weapon and toxic manifestations are not uncommon, and agranulocytosis often caused death. These may occur when the dosage is higher than that is required for maintenance therapy; they may still occur after months of administration. Mild temporary depression of leucocytes is common. Drug fever occurs in about 2 p.c. of all cases, generally during the first few weeks and should be regarded as the danger signal as it is a common manifestation of agranulocytosis and white cell count should be done immediately. Photosensitiveness, maculo-papular rash and urticaria may also appear. Nausea, dizziness, headache, thrombocytopenic purpura, swelling of the extremities though less frequent may appear.

PARATHYROID

Parathyroids regulate the calcium metabolism and increase the ionisable calcium content of the blood, and detoxicate certain metabolic poisons. Removal of the glands causes (*a*) lowering of the serum calcium, which may fall from 10 mg. to 5 or 6 mg. with symptoms of abnormal irritability of the muscular and nervous system and if the deficiency is continued may lead to symptoms of tetany; (*b*) diminished excretion of phosphates and consequent raising of the phosphate level in the blood. Administration of parathyroid raises the serum calcium, and since the absorption of calcium is not increased, nor its excretion diminished but rather increased (this occurs even after complete removal of the alimentary canal), the rise of serum calcium is attributed to the mobilisation of calcium from the soft tissues and bones. In fact after its use the bones become softer, and in growing animals and after fracture less calcium is deposited.

It has been suggested that the action of parathyroid is primarily on the kidneys, since when injected it causes first an increased excretion of phosphate and a lowering of blood phosphate, and that these effects always precede the rise of serum calcium. In fact Neufeld and Collip have shown that its injection in animals will not cause rise of serum calcium if the excretion of urine is prevented either by removal of kidneys or ligature of renal vessels or the ureters.

INJECTIO PARATHYROIDEI, U. S. P. (Inj. Parathyroid.).—Injection of Parathyroid.

Syn.—Parathyroid Extract; Parathormone.

Source.—It is a sterile solution in water for injection of the water-soluble principle or principles of the parathyroid glands which relieves the symptoms of parathyroid tetany and increases the calcium content of the blood serum in man and other animals.

One c. c. possesses a potency of not less than 100 U. S. P. units. Each unit represents 1/100th of the amount required to raise the

calcium content of 100 c.c. of the blood serum of normal dogs 1 mg. within 16 to 18 hours after administration.

Dose, U. S. P.—25 U. S. P. Units by *intramuscular injection.*

USES

The use of parathyroid is indicated in all clinical conditions characterised by low blood calcium provided the bones are not depleted of calcium. But the most important use is in **tetany** specially in post thyroidectomy patients. It is also useful in **spasmophilia, myasthenia gravis, paralysis agitans.** Since its administration is followed by diuresis, it has been used in oliguria, and anuria associated with glomerulo-nephritis specially when the blood calcium is lowered.

A single large dose has little effect, but repeated smaller doses show symptoms of hypercalcaemia by raising the calcium content of the serum to over 12 mg. per 100 mil which is not desirable or up to 20 mg. per 100 mil which is dangerous. Its administration is followed by vagotonia with slow pulse, hyperaemia of the abdominal organs and increased gastric and intestinal movements. It is administered by subcutaneous injection and its use should be controlled by determination of the calcium content of the blood to avoid hypercalcaemia.

In lead poisoning it is useful after the subsidence of acute symptoms as it helps liberation of lead with calcium. But large doses are required to produce this effect.

Except in cases where there is distinct deficiency of blood calcium, *i.e.* below 10 mg. per 100 mil its use in other conditions is at best a speculative one. As it mobilises the calcium from other tissues, mainly the bones and muscles to the blood, its use is contra-indicated in those conditions in which the object is to bring about deposition of calcium in the bones and not merely to raise the serum calcium, *e.g.* in rickets, osteomalacia, etc.

Toxic symptoms.—Parathyroid is a powerful drug and is cumulative, and repeated smaller doses show symptoms of hypercalcaemia by raising the calcium content of the serum to over 12 mg. or even 20 mg. per 100 mil. The symptoms of hypercalcaemia are restlessness, respiratory distress, muscular weakness, vomiting, loss of appetite, diarrhoea, impaired circulation, dullness, drowsiness, haematuria, collapse and death.

INJECTIO INSULINI

(Inj. Insulin.)

Syn.—Insulin.

Source.—Injection of Insulin is a sterile solution of the specific antidiabetic principle of the mammalian pancreas, containing 20, 40 or 80 Units per millilitre.

Characters.—Colourless liquid, free from turbidity and from matter which deposits on standing.

Storage.—It should be kept at as low a temperature as possible above its freezing point, and should not be exposed to temperature

above 20°C. when it will retain its potency for at least two years at reaction between pH 3 and pH 4.

The label should state (1) date of manufacture; (2) date after which it should not be used.

B. P. Dose.—*By injection.* The dose in determined by the physician in accordance with the needs of the patient. N. B. Ordinarily 20 Units per mil shall be dispensed, unless a solution of some other strength is specified.

Three units of insulin is the amount in c.c. which on subcutaneous injection into a normal rabbit weighing 2 kg. reduces its blood-sugar from the normal of 0.16 p.c. to 0.045 p.c. within 2 hours. At this point the rabbit develops coma and convulsion. The Unit is contained in 0.0455 mg. of the Standard Preparation in use in 1947.

Action and Uses

Insulin is the active principle of the pancreas, which is produced in the islets of Langerhans, and which being constantly secreted into the blood plays an important part in the metabolism of carbohydrate. Little is known of its nature and structure except that it is a protein and has a polypeptide structure. Eleven amino-acids have been recognised as combined in its molecule in definite proportions. It also contains 3.3 p.c. of sulphur as a disulphide linkage and can be accounted for as cystine.

Removal of pancreas in animals is followed by a rise of blood-sugar above normal and appearance of sugar in the form of dextrose in the urine. Since the glycosuria appears even in the absence of any carbohydrate food from conversion of other substances in the body into dextrose, the body gets depleted of sugar and the animal loses weight. There is a loss of glycogen from the liver and failure to utilise sugar, so that the metabolism of fats is also affected, and as a result of incomplete oxidation of fats there accumulates in the body *aceto-acetic acid* and *β-hydroxybutyric acid* which are excreted in the urine. There is also a fall in the respiratory quotient showing that all the oxygen used is not reappearing in the breath as CO_2, and increased excretion of urinary nitrogen indicating conversion of protein into carbohydrate. An injection of insulin will relieve these symptoms and restore the disturbed carbohydrate metabolism to normal.

Insulin helps the tissues to metabolise sugar and enables the liver and muscles to store glycogen and to utilise glucose as a source of energy. This improved combustion of sugar helps combustion of fats and corrects faulty metabolism thereby helping disappearance of ketone bodies and acidosis responsible for diabetic coma. Since injection of insulin in depancreatised dog, which is also given sugar, increases the respiratory quotient, it is evident that sugar is being oxidised, and it has therefore been suggested that insulin supplies the missing link, and by the control it exerts on the glycogenolytic ferment

permits of sugar being converted into a form suitable for oxidation. Insulin therefore is valuable in the treatment of **diabetes.** Under its use there is a marked reduction of the blood-sugar which remains at the normal level while the glycosuria disappears altogether. Along with the disappearance of sugar from the urine the ketone bodies usually disappear from the urine and blood within twenty-four to forty-eight hours, showing that fats are more efficiently dealt with. The carbohydrates are utilised more freely with a rise of respiratory quotient. In fact patients under insulin treatment show clear signs of improvement, and the cardinal symptoms of diabetes are relieved.

The best results are obtained in cases of threatened or actual **diabetic coma,** when larger doses (40 to 60 units) are given preferably by the intravenous route and as much as 200 units may be given in 24 hours. Since acidosis is the result of imperfect combustion of fats, it is necessary that fats should be withdrawn and carbohydrates in the shape of glucose administered, either by the mouth (30 to 40 grms. or 7½ to 10 drs.) or 20 mils (5 drs.) of 10 p.c. solution intravenously. Other measures such as rectal injection of 3 p.c. solution of sodium bicarbonate should be adopted. To be successful the treatment must be started early. A case in which the coma has existed for more than twenty hours without any improvement is hardly likely to recover under insulin. When large doses of insulin are administered glucose should also be given with it to prevent hypoglycaemia.

It has been used with success in the treatment of furunculosis not only when associated with diabetes but also in cases where there is no sugar in the urine but the blood-sugar content is high. Carbuncles in diabetics heal more rapidly under insulin treatment. Conditions depending on hyperglycaemia, *e.g.* neuralgia, pruritus, balanitis, etc., disappear under insulin.

Insulin is also of great value in **acidosis** and **ketosis** of non-diabetic origin. Thus **hyperemesis gravidarum** is successfully treated with injection of insulin and glucose. Similarly, cyclical vomiting of children is equally benefited by insulin and glucose. Its use has been suggested in exophthalmic goitre, it improves the goitre and exophthalmos and reduces the basal metabolic rate. As a prophylactic against acidosis prior to surgical operations and anaesthesia, specially in the diabetic, its value is undisputed.

Insulin increases appetite, gastric secretion and the secretion of bile and pancreas, and it has been used in **malnutrition** where it increases the weight in patients with intact carbohydrate metabolism, improves the subcutaneous tissue and gives a healthier appearance to the skin.

The method is to give 10 units three times before each meal the first day, and increasing by 5 units daily up to 20 to 30 units. It has been suggested that the good effects are due to (1) an increased demand for food ; (2) an improvement in the nutritive condition, causing an increased desire to eat ; and (3) training of the insulin-producing organs by carbohydrate administration to produce more insulin.

Insulin has also been used in **delirium tremens** in doses of 40 to 80 units to be followed immediately by administration of glucose. The best results are obtained when the patient does not receive glucose until after 2½ hours which he has spent in a soporose state, perspiring freely. One to four such treatments, of which two may be given in 24 hours, usually suffice for complete recovery. Insulin has been used in the treatment of **drug addiction**, *e.g.* during the withdrawal stage of morphine.

Convulsive Therapy.—Within recent years so-called "shock" treatment or induction of convulsion, as a therapeutic measure, has been utilised for the treatment of certain **mental diseases** of both diabetics and non-diabetics (schizophrenics). How they act is not clear. Insulin may be used alone to produce hypoglycaemic coma or with leptazol to produce convulsion. The method is to give insulin daily in the morning during fasting in increasing doses till hypoglycaemic coma appears. Commencing with 20 Units and increasing daily by 10 Units. The proper dose is reached when the patient becomes unconscious after three hours and passes into deep coma in the fourth or fifth hour. But the patient should not remain in the comatose stage for more than 45 minutes and should be brought back with the administration of glucose intravenously. The treatment is repeated either every day or on every alternate day for two to three weeks. When leptazol is used it is given intravenously in doses of 3 to 5 mils of a 10 p.c. solution first and if no convulsion is produced within one minute the dose is repeated with half to 1 mil more than the first dose but should not be more than 12 mil in all. This injection is given when the patient is in a state of hypoglycaemic coma, so that he avoids the unpleasantness of convulsion. To reduce severity of convulsion which often causes fracture of the spine or dislocations, it is often combined with curare. (*See* page 260). The treatment is not without danger and death has occurred in some instances from dilatation of the heart, coronary occlusion, ventricular fibrillation, pulmonary oedema and pneumonia.

Methods of administration.—Insulin has no action when given by the mouth or per rectum, as it is rapidly destroyed by the digestive enzymes. Within certain limits

perlingual administration may be successful, but cannot be regarded as a substitute for injection. It is doubtful whether absorption by the mouth is sufficient to replace subcutaneous injection, and in all cases where immediate effect is necessary it should always be given subcutaneously, or in urgent cases, intravenously. The usual dose for an adult is 10 units, repeated twice daily, and should be given a *quarter to half an hour before a meal* so that it can exert its effects on the glucose which reaches the blood from the meal. This precaution will prevent the risk of hypoglycaemia.

The dose of insulin depends upon

(1) the severity of the case ;

(2) weight, a heavier individual requires a larger dose ;

(3) amount of intake of food ; and

(4) septic or other complications. Infection in general diminishes carbohydrate tolerance.

Whenever possible the treatment should be controlled by blood-sugar estimation. If this is not practicable the dose of 20 units should not be exceeded. During insulin treatment the patient should not be allowed to fast too long after the injection. When the insulin requirement exceeds 40 to 50 units daily, it is better to divide it into two or three doses. The single dose method is unsatisfactory when the daily requirement exceeds ten units.

Before adopting treatment always make sure that the case is really one of diabetes. It is dangerous to treat cases like renal glycosuria where the blood-sugar is already low. It is desirable before adopting insulin treatment to try the effect of dieting, and when the patient is doing fairly well on diet insulin should not be given. If however the blood sugar still remains high on a maintenance diet, the additional carbohydrate requires to be metabolised by the administration of insulin. Since 1 unit of insulin will metabolise 1.5 to 2 grm. of glucose, a convenient method of determining the amount of insulin necessary is to divide the total quantity of sugar excreted by 1.5. Thus if the total quantity of sugar in 24 hours be 60 grm. then $60 \div 1.5 = 40$ units of insulin are required daily. This should be given in 2 or 3 divided doses half an hour before each meal.

Duration of action.—Insulin produces its effect within 15 minutes after an injection and reaches its peak in about 3 hours. When a very large dose is given at once, say 100 units, duration of its effect will be twice as long as that of ten units. Given intravenously the effect is almost immediate and the excretion also being very rapid, the maximum effect lasts only for an hour or two.

Result of overdosage.—A dose of insulin which will lower blood-sugar in rabbits to 0.045 p. c. or less causes

increased reflexes, rapid and shallow respiration, clonic convulsion, coma and death. In man the symptoms of hypoglycaemia are observed when insulin is given in very large doses, or when the supplement to the diet is not given in the proper time relation. The severity of the symptoms depends upon the fall of blood-sugar. When the blood-sugar content is 0.07 p. c. the patient only experiences a sense of uneasiness and nervousness with a feeling of impending danger. When it is below 0.06 p. c. there is weakness, nervousness, dizziness, disturbances of sight and profuse perspiration. If the sugar is reduced still further, *i. e.* 0.04-0.055 p. c., there is aphasia, disorientation, mental confusion, loss of reflexes, and perhaps coma and death. The symptoms are possibly due to defective supply of glucose to the nerve cells of the brain, and are rapidly removed by the administration of some carbohydrate. Insulin exerts its maximum effects about four to five hours after injection, therefore the symptoms of overdosage appears at this time. These symptoms are induced or aggravated by exercise ; and patients should be warned of this possibility and should be advised to keep some sugar preparation for an emergency. An ounce of glucose or other sugar solution may be given by the mouth.

If the patient is unconscious or the symptoms have lasted long, it is necessary that glucose should be given by intravenous injection, 5 to 20 grms. (75 to 300 grs.) being given in 50 to 100 mils ($12\frac{1}{2}$ to 25 drs.) of water. Adrenaline (15 ms. or 1 mil of the injection), which mobilises the glycogen of the liver, or pituitrin ($\frac{1}{2}$ to 1 mil) which antagonises the effect of insulin, may be given. But since the effect of adrenaline depends upon the availability of glycogen in the liver which may be present in very small amount, glucose should also be administered even if adrenaline is given.

Conclusion.—Insulin is not a cure for diabetes, but it is a valuable aid to the physician specially in cases of diabetic coma. It has helped diabetic patients to undergo surgical operations without any danger. The only drawback is that its effects do not last long, and it has to be used for an indefinite period, at least in some severe cases, while in others it fails to make the urine sugar-free.

The following conditions during treatment require modification of dosage :—

(1) *Acute infections*, like influenza and pneumonia, and *local septic conditions*, like boils, carbuncles and septic teeth, cause increased hyperglycaemia and ketosis, call for larger doses of insulin together with administration of carbohydrates, *e. g.* dextrose. (2) Hyperglycaemia may occur during the *latter half of pregnancy* requiring more insulin ; whereas after child-birth hypoglycaemia may develop necessitating either reduction or stoppage of insulin. (3) The dose should be cautiously increased to avoid sudden lowering of

blood-sugar in elderly persons with *heart disease*, or in those suffering from myocardial disease. The same caution is required in patients with a tendency to *angina*.

Insulin mixture.—Under certain circumstances soluble insulin may be combined with one of the slow acting preparations, advantage being taken of the rapid action of the one and the prolonged action of the other. This is specially indicated in patients who readily form acetone in the body. Experience has shown that slow acting insulin like protamine zinc insulin or globin zinc insulin are less effective in controlling ketosis than unmodified insulin.

The importance of distinguishing diabetic coma from insulin coma is obvious, and Graham * gives the following points for distinguishing them :—

Insulin Coma	Diabetic Coma
1. Skin usually very white, may be normal in colour.	Skin usually flushed.
2. No smell of acetone in breath.	Breath smells of acetone.
3. Respiration shallow.	Respiration deep (abdominal respiration is characteristic).
4. Urine usually sugar-free except when bladder was not emptied for some hours or blood-sugar was above 200 mg. per 100 c. c.	Always contains large amount of sugar.
5. Eyeball tension normal or raised.	Eyeball tension much lower.
6. Urine need not contain aceto-acetic acid.	Urine always contains large amounts of aceto-acetic acid.
7. Blood-sugar below 70 mg. per 100 c. c., may be below 40 mg.	Blood-sugar over 200 mg. per 100 c. c. may be even 500-800 mg.

Injectio Insulini Protaminati cum Zinco. Syn.—Protamine Zinc Insulin.—Injection of Protamine Zinc Insulin is a sterile suspension of the specific antidiabetic principle of the mammalian pancreas, with a suitable protamine and zinc chloride, containing 40 or 80 Units per millilitre.

Characters.—An almost colourless turbid liquid. It should be kept under the same conditions as Injection of Insulin.

The label should state (1) the date of manufacture ; (2) the date after which the preparation is not intended to be used ; (3) that the containers should be carefully shaken before a dose is withdrawn.

B. P. Dose.—*By injection.* The dose is determined by the physician according to the needs of the patient. N. B. When this injection is prescribed, Protamine Zinc Insulin containing 40 units per mil shall be dispensed, unless a preparation of some other strength is specified.

PROTAMINE INSULIN. (Not official). Syn.—Insulin Retard.—A compound of insulin hydrochloride with a protamine obtained from the sperm of a species of trout. It is injected as a colloidal suspension formed by the addition of sodium phosphate which precipitates protamine insulin with a *p*H of 7.3.

ACTION AND USES

It has been pointed out by Hagedorn that insulin like other proteins precipitates with protamine. When this sus-

* Graham, *Medical Press and Circular*, 1934, Symposium, No. 1.

pension is used it causes a more prolonged fall of blood sugar. Later Scott and Fisher showed that the addition of zinc further prolonged the action of protamine insulin. Protamine-zinc-insulin is therefore used in those cases where the original insulin requires to be administered in several doses daily, or it causes frequent hypoglycaemic reactions. Whereas maximum reduction of blood sugar with unmodified insulin takes place in about 2 to 3 hours, the greatest effect of protamine-zinc-insulin does not develop till after 6 to 10 hours, and the effect lasts for 24 to 30 hours. The fall of blood sugar is therefore gradual and the rapid alteration of blood sugar level which follows the administration of original insulin is obviated. Since its absorption is slow and the effects do not show themselves till several hours after administration, it cannot control a carbohydrate meal taken soon after the injection. It is therefore necessary sometimes to give an injection of soluble insulin before breakfast to deal with the blood sugar rise from this meal and then administer protamine-zinc-insulin to maintain the sugar within normal level during the rest of the day.

Protamine-zinc-insulin may be administered once a day either in the morning, one and one-half hours before breakfast, or one hour before the last meal, or an hour before retiring, or half the required dose may be given in the morning and the other half in the evening.

When treating patients with protamine-zinc-insulin, owing to the slow action, the full effect of the treatment will not be observed until a week or two after the initial administration. Therefore one should not increase the dose if no benefit is observed during the first few days of its administration.

Protamine zinc insulin hypoglycaemia.—Hypoglycaemic reactions after this remedy is not so frequent as after the use of unmodified insulin. Owing to its slow action these come on very slowly and are often missed, due to the symptoms being less definite. Vague symptoms of fatigue, headache, drowsiness, lassitude, tremulousness, and nausea should be looked upon with suspicion. The typical symptoms of hypoglycaemia following ordinary insulin may however appear suddenly with some patients. The appearance of any of these symptoms calls for immediate treatment and since the supply of insulin to the tissues is slow and continuous the treatment must be prolonged.

Globin Zinc Insulin.—It is prepared by combining insulin with globin derived from haemoglobin of beef-blood with zinc chloride, and is a clear solution. It begins to show its effect in two hours, reaches maximum between five to eight hours and lasts for fifteen to twenty-four hours. Because of the slow onset it is administered 45 to 60 minutes before meals in the morning so that in case of

hypoglycaemic reaction it will appear in the afternoon. It is desirable therefore, to have a mid-afternoon meal. When changing from soluble to globin insulin, the first dose should be about two-third of the unmodified insulin ; while shifting from protamine zinc insulin, not more than half the initial dose should be used. *It should not be given intravenously* as it is precipitated in the blood and is of no value in emergencies. One mil contains 40 Units.

Guanidine. (*Not official*).—Guanidine is found in certain plants and can also be obtained from certain proteins. It resembles physostigmine in action and causes fibrillary muscular twitchings. This effect is antagonised by curare and occurs after the nerve-endings have been cut but not after they have degenerated. The effect is due to the stimulation of the same myoneural receptors as are affected by physostigmine.

Guanidine has been used in **myasthenia gravis** with sustained improvement and may be administered either intravenously (2 p. c. solution in normal saline) or by the mouth in capsules. It should first be given in doses of 10 mg. (1/6 gr.) per kilo of body weight to test its effectiveness. Patients suffering from myasthenia gravis tolerate larger doses for a long period. Sometimes it is combined with neostigmine.

It has however the property of reducing blood-sugar and producing hypoglycaemia. Subsequently Frank and others introduced Synthalin and Synthalin-B, both guanidine derivatives, with properties similar to those of insulin, but without its toxic effects and which unlike insulin are effective when administered by the mouth. How synthalin acts is not known, but it is possible that it acts either by lowering the cellular threshold for glucose-insulin metabolism, or more probably, by depressing glycogenolysis, thereby increasing the secretion of endogenous insulin. It is extolled by some but so far the results have not been uniform.

Some patients show intolerance to synthalin. The symptoms are vague dyspepsia, feeling of weight in the upper abdomen, flatulence, constipation or often looseness with colicky pain, loss of weight and general malaise and languor. These symptoms are rare when a high carbohydrate and a low fat diet is given.*

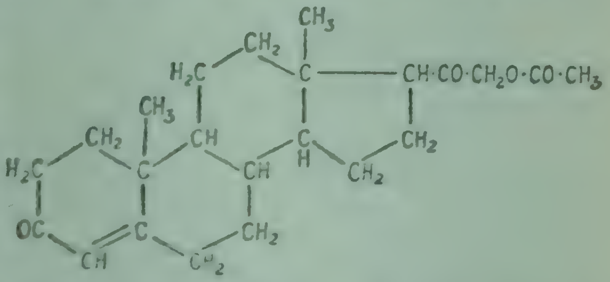
Synthalin.—Decamethylene-guanidine dihydrochloride. *Dose.*—1/6 gr. or 10 mg.

Synthalin-B.—Dodecamethyl guanidine hydrochloride. *Dose.*—1/12 gr. or 5 mg.

DEOXYCORTONI ACETAS

Syn.—Desoxycorticosterone Acetate ; DOCA ; Desoxycortone Acetate ; Percorten.

Source.—Deoxycortone Acetate is 21-acetoxy-Δ^4-pregnene-3 : 20-dione. In colourless crystals or crystalline powder; odourless. *Insoluble* in water, soluble in alcohol (95 p. c.), in acetone and in fixed oils.



B. P. Dose.—By intramuscular injection :—1/30 to 1/6 gr. or 2 to 10 mg. Total implantation dose :—2 to 6 grs. or 0.2 to 0.4 grm.

OFFICIAL PREPARATION

1. Injectio Deoxycortoni Acetatis.—A sterile solution in Ethyl Oleate or a suitable oil. B. P. Dose.—1/30 to 1/6 gr. or 2 to 10 mg. by intramuscular injection. N. B. When no strength is stated, 1/12 gr. in 15 ms. shall be dispensed.

* Todd, [illegible] and Sansom, *The Practitioner*, May, 1932.

INJECTIO SUPRARENALI CORTICIS, B.P.C. Syn.—Extract of Suprarenal Cortex; Cortin; Eucortone.

An extract containing the specific principle of suprarenal cortex which when injected, prolongs the life of cats or dogs from which the glands have been removed.

Composition.—Contains a number of steroid compounds, the important ones are : *corticosterone*, *dehydrocorticosterone* and *deoxycortone*. Contains no ascorbic acid and only a trace of adrenaline.

Dose.—75 to 600 ms. or 5 to 40 mils, by *subcutaneous*, *intramuscular* or *intravenous injection.*

Action and Uses

In 1856 Brown-Seqúard following the classical description of the clinical picture of chronic adrenal insufficiency (Addison's disease) attempted to reproduce the Addisonian syndrome in animals. The rapidly fatal results (the animals only survived for a few hours) led him to conclude that the adrenals were indispensable to life.

The chief functions of the cortex may be summarised as follows : (*a*) It maintains normal blood volume by control of excretion and resorption (in the kidney tubules) of electrolytes and water, *i.e.* controls retention of sodium and excretion of potassium ; (*b*) it acts as a general tissue and cell catalyst, specially with regard to the hepatic function ; and (*c*) it is essential for the normal carbohydrate metabolism and its absence or deficiency causes hypoglycaemia with decrease of muscle and liver glycogen.

The activity of the cortex is controlled by the adrenotrophic hormone of the anterior pituitary. Several steroid substances have been isolated from the cortex. Of these deoxycortone is primarily concerned with mineral metabolism and water balance, while corticosterone and 17-hydroxy-11-dehydrocorticosterone (cortisone) affect carbohydrate metabolism and promote gluconeogenesis.

There is evidence to indicate that it is closely related to urea formation, to cholesterol metabolism, and to resistance to infection and toxaemia. It is rich in ascorbic acid than any other tissue of the body. In fact it is believed that it synthesises ascorbic acid. Some believe that it is a factor in the normal healing of wounds and callus formation. It is possible that it causes leucocytosis and strengthens their phagocytic activity.

Its deficiency, as observed in Addison's disease or in experimental animals, produces increased excretion of sodium in the urine and corresponding reduction of bicarbonate and chloride of sodium in the blood and tissues ; increase of potassium and urea nitrogen in the blood and lowering of blood volume and loss of body weight ; hypoglycaemia ; great muscular weekness ; low blood pressure ; abnormal pigmentation and susceptibility to infection. The most serious defect of adrenal deficiency is loss of sodium due to the inability of the renal tubules to reabsorb it. There is extreme loss of fluid and the body suffers from

dehydration. The basal metabolic rate is diminished to the extent of 25 p.c.

The cortex is also intimately related to the sexual organs, and its over-activity inhibits the development of female sex glands. Women suffering from tumours of the cortex show signs of virilism, hirsutism and atrophy of the breast and uterus and in children causes precocious sex development.

It is largely used in the treatment of Addison's disease which is associated with degenerative changes in the cortex, and it supplies the hormone absent in this disease. Its administration is followed by the disappearance of nearly all the signs and symptoms of the condition. The blood potassium falls, blood pressure and renal function return to normal. An important point to remember is that during treatment there should be no restriction to potassium, as otherwise it may fall far too low to cause partial paralysis, on the other hand over administration of deoxycortone may increase sodium retention with oedema. The usual method of treatment is either to administer the extract of the gland subcutaneously, intramuscularly or intravenously, 10 to 20 mils (150 to 300 ms.) daily in divided doses with sodium chloride 5 to 20 grms. (75 to 300 grs.) either by the mouth or by injection. This should be followed by *maintenance dose* of 75 to 150 ms. (5 to 10 mils), subcutaneously or intramuscularly every 4 to 8 hours, supplemented with administration of sodium chloride. Deoxycorticosterone acetate (DOCA) injection may be used in doses of 5 to 10 mg. (1/12 to 1/6 gr.). With this the effect is observed within half to one hour after administration. To avoid daily injection and for prolonged action cylindrical pellets may be implanted into the deep subcutaneous tissue in doses of 25, 50 and 100 mg. when the effect will be maintained for three to nine months.

Because the symptoms of adrenal cortical insufficiency are not unlike histamine shock or shock due to burns, both cortin and desoxycorticosterone have been used in the treatment of **surgical** and **traumatic shock** and in the shock and acute toxaemia of burns with benefit. Since the loss of blood volume is associated with the collapse of **cholera**, cortin may be used in this condition with hypertonic saline infusion. Percorten either by injection or by implantation has been followed by striking benefit in **myasthenia gravis**.

Its use has also been suggested in **cyclical vomiting, infantile diarrhoea** of uncertain origin, **vomiting of pregnancy, and severe infection.***

Caution.—Desoxycorticosterone used in large doses may give

* Kemp, *British Medical Journal*, June 12, 1937.

rise to hyperglycaemia, retention of sodium chloride and oedema, and hypertension with congestive heart failure.

CORTISONE

Cortisone or Compound E is 17-hydroxy-11-dihydrocorticosterone. The fact that rheumatoid arthritis is often relieved by pregnancy or development of hepatitis with jaundice, and the fact that temporary remission of the disease follows such procedures which stimulate adrenal cortex, *e.g.* general anaesthesia and surgical operation, led to the belief that the antirheumatic agent might be a hormone of the adrenal cortex. Cortisone has, therefore, been used in the treatment of **rheumatoid arthritis** *intramuscularly* in **doses of 100 mg.** *per day* in the form of acetate. The first improvement observed is characterised by loss of joint stiffness followed by a sense of well-being. As the treatment is prolonged the pain becomes less and there is increased range of movement of the joint with fall of eosinophils in the blood and decreased sedimentation rates. The treatment requires to be prolonged according to the condition of the patient and by giving a daily **maintenance dose** which has to be adjusted. Cortisone should not be considered as the treatment of choice in most cases of rheumatoid arthritis and not as a cure for any case.

Good results followed its use in **lupus erythematous** and **gouty arthritis.** In gout it increases excretion of uric acid and there is fall in the serum uric acid level with improvement of joint movements, diminished pain and softening of tophi.

Apart from its value in rheumatoid arthritis, the use of cortisone has been extended to other conditions involving the collagen tissues of the body. Thus it has been used in **rheumatic fever** where its use is followed by disappearance of the fever, tachycardia and polyarthritis with diminution of the sedimentation rates. It has been suggested that cortisone produces definite effect on the cardiac muscle and the valves. Usual dose is 100 mg. twice daily and then 50 mg. twice daily. It often relieves **asthma** and may also produce temporary remission of *lymphatic leukaemia, lymphosarcoma* and *Hodgkin's disease.* These effects are due to special property of the drug of reducing the number of circulating eosinophils and lymphocytes in the blood.

ADRENOCORTICOTROPHIC HORMONE (ACTH).

Since the activity of adrenal cortex is stimulated by the adrenocorticotrophic hormone of anterior pituitary, which induces increased secretion of cortisone, adrenocorticotrophic hormone (ACTH) has been used with equally good results in rheumatoid arthritis, rheumatic fever, lupus erythematous, asthma and gouty conditions. The **dose is 80 mg.** ($1\frac{1}{3}$ gr.) daily every six hours, i.e. **20 mg.** (1/3 gr.) at a time by intramuscular injection. ACTH and adrenal cortical extract (ACE) have been found effective in the treatment of acute alcoholic intoxication; while dramatic results follow the administration of ACTH in delirium tremens, it is not of much value in Korsakoff's psychosis where ACE is effective.

MUSCLE EXTRACT

Within recent years extract of mammalian tissue has been used in the treatment of cardiac and circulatory disturbances. A preparation called **Lacarnol** (extract of heart muscle) has been placed on the market and is claimed that it has a specific action in dilating the vessels, specially coronary arteries. The indications for its administration are cardiac failure, arrhythmia, angina pectoris, intermittent claudication, and (occasionally) hypertension. There is evidence that muscular exertion liberates antispamodic and vaso-dila-

tor substances, which sometimes prevent anginal attacks or intermittent claudication. Muscle extract is specially useful in spasmodic angina; attacks due to cardiac dilatation or coronary thrombosis are seldom if ever relieved. Apart from these vaso-dilator and antispasmodic effects, muscle extracts appear to have a cardiotonic and regulating action, relieving decompensation and arrhythmia. The action sometimes resembles degitalis, in fact the effect is very definite when both are given in combination.

It may be used both *hypodermically* and by *mouth*. The *dose* of Lacarnol is 10 to 25 drops once or thrice daily, or 1 mil hypodermically. Another preparation is Sarcolan, dose 1 mil hypodermically.

GROUP XXI

DRUGS ACTING ON THE BLOOD

Changes in the blood both in quality and quantity may occur necessitating the use of remedial measures. The most important change occurs with regard to the red blood cells. They may be diminished in number, or there may be deficiency of haemoglobin, and since the oxygen-carrying power of the blood depends upon the amount of haemoglobin in the corpuscle, deficiency of red blood corpuscles and haemoglobin, *i.e.* anaemia demands early treatment. Iron is its chief constituent and the body contains about 3 to 4 grms., and about two-third of the iron in the body, *i.e.* 2.4 to 2.7 grms. exists in the form of haemoglobin, the rest is stored in the liver, spleen and other tissues by the reticulo-enothelial cells.

Normally the red blood corpuscles have an average life of about 120 days, hence they require constant renewal to maintain the red blood cells at the normal level. About 100 mg. of iron is liberated daily from such destruction and this iron is retained in the body as *haemosiderin granules* within the reticulo-endothelial cells, and utilised in the formation of new red cells. Drugs which increase the number of red blood corpuscles and haemoglobin to normal level are known as **haematinics.**

Haematinics have no effect in increasing the amount of iron in healthy blood. They act only when either the haemoglobin or the number of red corpuscles are deficient. The red blood corpuscles are manufactured in the red bone marrow. Anaemia occurs when the bone marrow fails to keep up with the demands of the body and many factors are responsible for this and these may act separately or together. Arsenic causes hyperaemia of red bone marrow, and liver extract causes increased formation of red blood cells. Iron and its salts, and desiccated stomach are also **valuable haematinics.**

In order that the student may understand the rational treatment of anaemia it is necessary that he should have a clear conception of the underlying factors which produce the condition. It is also essential that a thorough investiga-

tion should be made of the underlying causal factors. If the causal factor is not removed, the chances are that the treatment will fail inspite of the use of appropriate haematinics.

Recent studies have brought to light the different factors which control the formation of the red blood cells in the bone marrow. A special haematinic (anti-anaemic) principle (recently identified as Vitamin B_{12}) is necessary for the development of the megaloblast to the erythroblast stage, and the relationship of iron in the transformation of the erythroblast into a mature erythrocyte has long been recognised. Small quantity of copper is necessary for the synthesis of haemoglobin, while thyroxine and vitamins B and C are also of value in helping formation of red cells.

Anaemia has been classified broadly into the following groups :—

A. *Macrocytic Hyperchromic Anaemia.*—Pernicious anaemia is the typical example of this variety, and is characterised by a reduction in the number of red cells, which become abnormal in shape and size (tend to become larger), but the haemoglobin is correspondingly less diminished so that there is a high colour index (hyperchromic). The blood maturing function of the red bone marrow is disturbed from the absence of the antianaemic principle which is stored in the liver. This principle is formed in the stomach by the interaction of an enzyme present in the gastric juice (*intrinsic factor* or *haematinic principle* of Castle), with another substance present in meat, yeast and other foods and possibly vitamin B complex (*extrinsic factor*). This specific antianaemic factor is stored in the liver and after interaction with bone marrow forms normal blood. The nature of the antianaemic factor in the liver is not known, they are possibly vitamin B_{12} and folic acid. It follows therefore that any breakdown in the above chain will cause macrocytic anaemia as a result of the failure of megaloblastic maturation.

(*a*) The breakdown may be in the intrinsic factor due to failure of the stomach to secrete the special enzyme. Possibly responsible for Addisonian pernicious anaemia.

(*b*) The breakdown may be in the extrinsic factor. Malnutrition (absence of high grade proteins and fresh vegetables) specially in the tropics is an important factor in the production of megalocytic hyperchromic anaemia. The anaemia of pregnancy is believed to be due to the absence of this factor and is successfully treated with proper diet and autolysed yeast.

(*c*) Both factors may be present, but owing to the abnormal state of the intestinal canal it may fail to absorb and utilise the haematinic principle. This possibly occurs in the presence of intestinal parasites or when there is impermeability of the intestinal mucosa. Faulty absorption of the haematinic principle is perhaps the cause of the failure to respond to liver administered by the mouth, though these cases improve when administered by intramuscular injection.

According to Castle* all the above factors are at work in tropical sprue.

(*d*) Faulty storage of the haematinic principle (P.A. Factor). It is possible that associated with this fault there is also mineral deficiency, and these cases improve when iron is given with liver.

**Lancet*, 1932, Vol. 1.

In cases of megalocytic hyperchromic anaemia associated with intestinal lesion this dual deficiency may be present.

B. *Microcytic Hypochromic Anaemia* or *Iron Deficiency Anaemia.*—This is primarily due to iron deficiency either in the diet, *e.g.* nutritional anaemia of infants ; or when absorption of iron is defective consequent on achlorhydria (chlorosis falls under this group), or when there is increased demand for iron, as in pregnancy, menorrhagia, etc. In fact all anaemias occurring as the result of or as an accompaniment of some disease can be classified as microcytic hypochromic anaemia. Characteristic feature of this type of anaemia is decrease of haemoglobin more than the number of red blood cell. It stands to reason that since this type of anaemia is secondary to some disease the real causative condition should be discovered and properly treated first, unless of course the condition has advanced much and requires immediate treatment.

A mild form of anaemia of this variety may occur in thyroid deficiency, which is cured by a course of thyroid. Iron and copper, also vitamin C are necessary for the transformation of erythroblasts to erythrocytes.

The anaemia of pregnancy may be of the microcytic type from deficiency of iron in the diet, or from defect in the absorption of iron from disturbances in the stomach and intestine, or from excessive drainage of iron. These improve under iron. But the intrinsic factor may also be involved leading to the pernicious type of anaemia.

C. *Normocytic Anaemia.*—This is characterised by diminution not only of the red cells but also corresponding decrease of the haemoglobin, the red blood cells remaining normal in size. The common example of this type of anaemia is that which follows profuse bleeding. Under ordinary circumstances this blood loss is not much and regeneration takes place without any treatment with any haematinic. Treatment is the same as that of iron deficiency anaemia.

D. *Aplastic anaemia* is a condition where the activity of the bone marrow is entirely suspended, and generally follows the use of certain drugs, *viz.*, lead, mercury, benzene, etc. Arsenic causes some hyperaemia of the red bone marrow and is often used, although its exact mode of action is not known. Repeated transfusion of blood has been recommended in the hope that the bone marrow may regain its haemopoietic functions.

The bone marrow is concerned in the development of the red blood corpuscles, white blood corpuscles (mainly granulocytes) and blood platelets. Severe intoxication leads to aplastic anaemia which interferes with the formation of white blood cells, causes leucopenia and later agranulocytosis. Benzene reduces the formation of red and white blood cells and also blood platelets. X-ray and radium and bacterial toxin also cause damage to the bone marrow.

Polycythaemia.—Just as the number of red blood cells may be deminished producing anaemia, there may be excess of red blood cells producing polycythaemia. This condition may occur as a compensatory response, as in high altitudes, but may be pathogenic, when the condition is known as *polycythaemia vera* and occurs from involvement of the red bone marrow. The number may be as much as 8 to 14 millions per c.mm. and show no sign of irregularity in shape nor there is any increase of reticulocytes. Symptoms are weakness, lassitude, vertigo and cyanosis. Drugs used are phenylhydrazine hydrochloride and radioactive phosphorus.

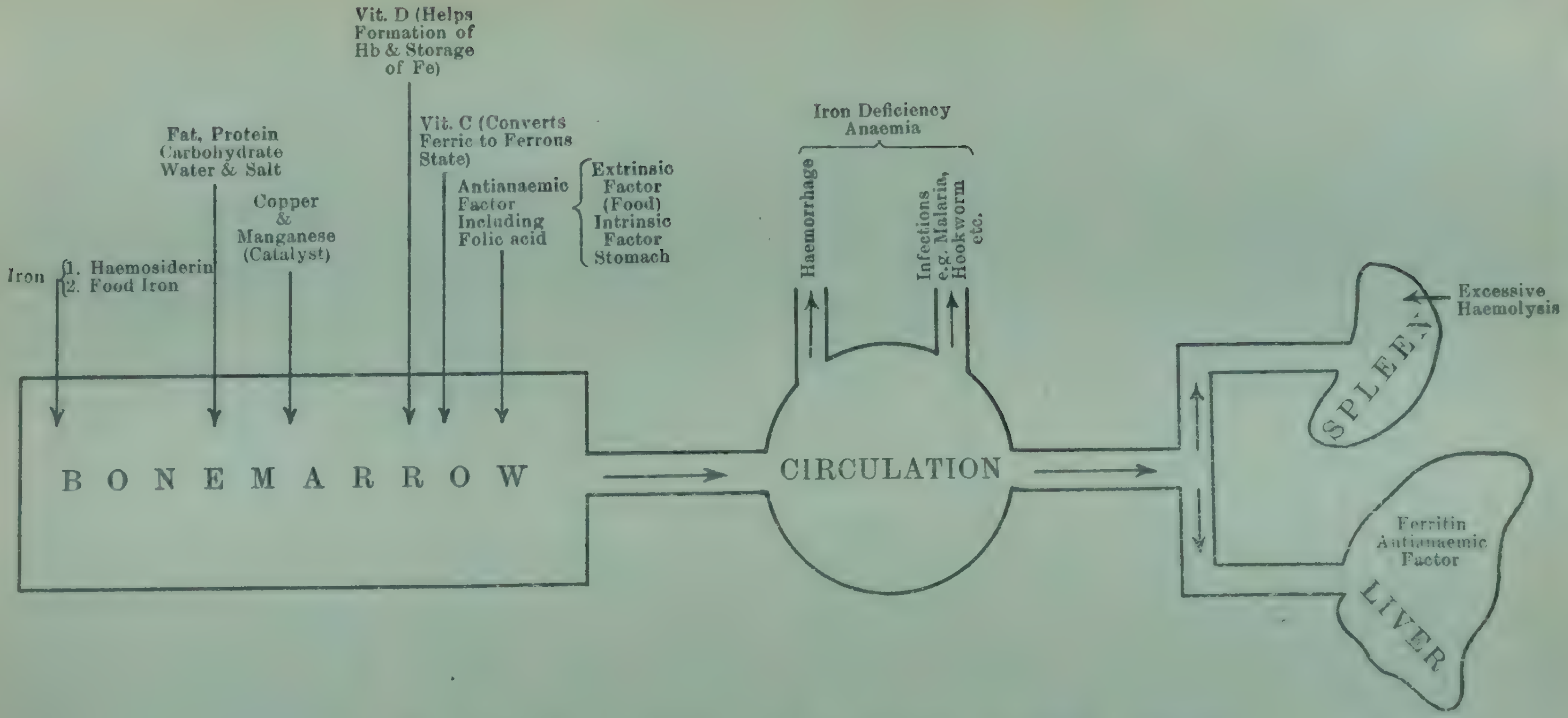


Fig. 37.—Haemopoiesis and Haematinics. Showing different factors concerned in the formation of red blood cells.

White Blood Corpuscles.—The white blood corpuscle differs from the erythrocyte in that it does not contain any haemoglobin, but contains a well-formed nucleus. Majority of them are much larger than the red cells but their number is less. Normally their number varies from 6000 to 8000 per c.mm. of blood, and this number may vary. In infancy and childhood their number is more than in adults.

The white blood cells have been divided into three groups, *viz.*, (*a*) *granulocytes*, of which there are three types depending upon the staining reactions of the granules, *viz.* (i) *eosinophilic*, (ii) *basophilic*, and (iii) *neutrophilic* ; (*b*) *lymphocytes*, these may be large and small ; and (*c*) *monocytes*. Lymphocytes and monocytes are non-granular under ordinary methods of staining.

Function.—The chief function of white blood corpuscle is to participate in the resistance of the body to infections. The neutrophilic polymorpho-nuclear leucocytes, the monocytes and other reticulo-endothelial elements form the most important defensive mechanism against invading micro-organisms. They have the property to ingest foreign particles and dissolve them by means of trypsin-like enzyme, a property known as *phagocytosis*.

Changes in the white blood corpuscle.—These may increase or diminish in number. An increase in the total leucocytes above 10,000 per c.mm. circulating in the blood is known as *leucocytosis*. All varieties of white cells do not necessarily share in the increase. Commonly, however, an increase of neutrophils is responsible for leucocytosis. Acute infections by the pus-forming organisms cause an increase of neutrophils. It also occurs in pneumonia, whooping cough and some infectious fevers.

In certain blood diseases, *leukaemia*, an enormous increase of white cells is an important characteristic and is pathological. In this condition the number of white cells may increase up to 1,000,000 per c.mm. and the red cells reduced. There are two forms depending upon the particular type of white cell predominating in the blood, viz., *myeloid leukaemia* and *lymphatic leukaemia*.

Treatment of leukaemia has been disappointing. Radioactive phosphorus (*see* page 133) has given encouraging result. Urethane (page 211) and arsenic as Fowler's solution (page 522). Recently mustine (nitrogen mustard) and folic acid antagonists have been introduced.

Leucopenia—This means reduction of the number of circulating leucocytes generally below 5,000 per c.mm. Ordinarily there is a decrease of neutrophil cells. A temporary fall in the leucocyte count may precede leucocytosis. Benzol causes leucopenia by depressing the activity of bone marrow.

Agranulocytosis or granulocytopenia is the term applied to an abnormally low leucocyte count due to the reduction in granulocytes. In 1922 the term *agranulocytic angina* was given to a condition characterised by inflammation of the throat (ulcerative angina), extreme prostration and high death rate with severe leucopenia (2000 or even less than 1000) and complete absence of granulocytes. It has been suggested that the condition might be due to depression of bone marrow caused by some micro-organism or to some chemical agent. The bone marrow may show either complete absence of granulocytes or their precursors, or a myeloblastic reaction, in which more myeloblasts than normal are produced but which do not mature. This condition may result in severe infection or as a result of certain drugs to which the person may be hypersensitive. It is possible that the phenomena may be allergic.

Several drugs produce this condition. They are amidopyrine, sulphonamides, thiouracil, organic arsenicals and gold salts.

Agranulocytosis has a high death rate and the mortality is due not directly to the condition but to secondary infection, since in the absence of leucocytes, the tissues have little defence.

Because of the high mortality rate and since some of the drugs which cause the condition are extensively used, the effective treatment of agranulocytosis is of great importance. The essential part in the treatment is (1) immediate withdrawal of the offending drug ; (2) administration of drugs like pentose nucleotide (as injectio nucleotidi), pyridoxine hydrochloride, folic acid, liver extract and penicillin ; and (3) blood transfusion.

The plasma.—The chief function of the plasma is to carry nutrient materials, hormones and drugs to the different tissues, and the excretory products to the kidneys. The plasma proteins help conversion of fibrinogen into fibrin when blood is shed. By exerting an osmotic pressure they tend to retain fluid in the capillaries and help to maintain the blood volume, regulate interchange between the blood and the tissue spaces and influence the filtration in the glomeruli in the kidney. The plasma contains and can develop immune bodies, *e.g.* agglutinins, precipitins, opsonins, etc., and obviously is of great value both in health and disease.

Reaction of the blood.—The normal reaction of the blood is almost neutral or weakly alkaline with a *p*H of 7.3 to 7.5 and life is incompatible when the *p*H of blood is below 7.0 or above 7.8. The maintenance of the *p*H at its normal level in the blood and tissues is regulated by the carbonates and alkaline phosphates which form the alka-

line reserve, and by the carbonic acid, the phosphates and proteins which form the acid reserve. The body is protected from the harmful effects due to variations of reaction not only by the buffer action of these salts, but also by the lungs, kidneys, and probably the intestine. The lungs get rid of the excess of CO_2 and the volatile acids (oxybutyric acid series) and the kidneys by increased excretion of fixed acids, and by increased ammonia formation.

Acidosis.—By acidosis is meant a condition in which the reaction of the blood is less alkaline than normal, and the blood is taken as an index of the reaction of the tissues generally. This may happen when the alkaline reserve of the body is depleted. Acids are always being produced in the body as a result of katabolic activity, but provision is made for their neutralisation and excretion through the buffer action of the blood and tissues and the excretory functions of the lungs and the kidneys. So long as this production of acid remains within normal limits and the organs concerned in its removal are functionating, there is no evidence of their disturbance. Of the acids, phosphoric, sulphuric and lactic and the other organic acids are neutralised as soon as they are formed, so that they are always present in the blood and tissue fluids as salts. CO_2 on the other hand is not completely neutralised and is found in the blood as a free acid in solution. In herbivorous animals owing to their food being rich in potassium and sodium, the acids are eliminated as salts of fixed alkalies, and the blood becomes depleted of its store of fixed alkalies when a large amount is lost. In carnivorous animals and in man there is no such loss as the acids are excreted in combination with ammonia, because their food contains little fixed alkalies and the acid products of metabolism are neutralised by ammonia liberated by the tissues thus protecting the fixed alkalies. In acid poisoning therefore ammonia salts excreted by the urine are increased. This protection is normally present but may fail when there is increased production of acids, as in diabetes due to defective oxidation of the products of fat metabolism resulting in the accumulation in the body of substances known as ketone bodies, *viz.*, aceto-acetic acid and β-hydroxybutyric acid (ketosis) ; in nephritis from diminished excretion of acid ; after exercise, and in arsenic and phosphorus poisoning from excessive production of lactic acid ; by the use of large doses of ammonium and calcium chloride ; or by adding to the body one of its acid elements, *viz.*, chlorine. Interference with the excretion of CO_2 by the lungs so that it may combine with water to form carbonic acid (H_2CO_3) which dissociates to yield H-ion, also increases the hydrogen-ion concentration of the blood. Minor degree of acidosis is also present after fasting speci-

ally with a low carbohydrate diet, in chloroform narcosis, etc. The term ketonaemia or acetonaemia signifies the presence of ketone bodies in the blood above 3.0 mg. per cent. and ketonuria or acetonuria their presence in the urine.

Alkalosis.—By this is meant a condition in which the blood is more alkaline than normal. Owing to the ease with which the body can accumulate acids, alkalosis is not so common as acidosis, but a mechanism exists to prevent the reaction of the blood and tissues from becoming too alkaline. It occurs clinically in persistent vomiting and in high intestinal obstruction and pyloric obstruction and to loss of hydrochloric acid, so that there is uncompensated acid deficit and accumulation of bicarbonates ; by forced breathing, thereby eliminating an excess of CO_2 from the alveolar air thus lowering the CO_2 tension in the arterial blood ; calcium deficiency, as after parathyroidectomy or tetany ; and by the use of large doses of alkalies as may happen in the treatment of peptic ulcer, provided the kidney function is impaired. Symptoms of alkalosis are : nausea, distaste for food, headache, weakness. Severe forms are followed by tetany, oedema and delirium.

Toxicology of blood.—Certain drugs like arsenious acid, phosphorus, iodine, sulphur, oil of turpentine and hydrocyanic acid reduce haemoglobin in poisonous doses. Phenazone, phenacetin and acetanilide, potassium chlorate and nitrites convert a portion of haemoglobin into methaemoglobin causing breakdown of corpuscles in poisonous doses. Inhalation of CO gas helps formation of carboxyhaemoglobin.

Sulphanilamide and some of its derivatives help formation of methaemoglobin and sulphaemoglobin. In fact drugs which normally form methaemoglobin also form sulphaemoglobin in the presence of sulphides.

Porphyrin is found in the urine making it red. It occurs in sulphonal poisoning, and may also appear after lead, alcohol, arsphenamine, various sulphonamide derivatives and antipyrin. Observations of the presence of porphyrin in the urine of animals is a convenient method of studying the toxic effects of drugs on the blood pigment and gives an idea of its toxicity in man.

Haemolysis or destruction of red blood cells occurs when the osmotic pressure of the surrounding fluid becomes lower than the corpuscles, as happens when the blood is greatly diluted with pure water. Conversely haemolysis may occur if the blood corpuscles have a higher osmotic tension than normal plasma, as happens when concentrated salt solution or pure glycerin is injected into the tissue. Besides the osmotic changes, saponins, ether, chloroform in sufficient concentration act as haemolytics. In practical therapeutics this is unimportant as saponins do not enter the blood unchanged from the intestine, and the narcotics do not reach the blood in sufficient concentration to produce any haemolytic effect.

As a result of haemolysis the glomeruli of the kidneys become blocked with the broken red blood cells and debris causing anuria. Moreover, if large amount of haemoglobin is excreted through the kidneys, these are precipitated in the tubules unless the urine is kept alkaline.

Class A : Drugs used in Macrocytic Hyperchromic Anaemia

EXTRACTUM HEPATIS LIQUIDUM

(Ext. Hepat. Liq.)

Liquid Extract of Liver is a selected fraction of an alcoholic extract of ox or sheep liver, dissolved in a mixture of glycerin, alcohol and distilled water.

Contains the specific principle which increases the number of red corpuscles in the blood of persons suffering from pernicious anaemia. 1 oz. is equivalent to 8 oz. of fresh liver.

B. P. Dose.—1 oz. or 30 mils.

NON-OFFICIAL PREPARATIONS

1. **Liquor Hepatis, U. S. P.**—Liver Solution is a brownish liquid, and contains that soluble thermostabile fraction of mammalian livers which increases the number of red blood corpuscles in persons affected with anaemia. *Average Dose, U. S. P.*—One U. S. P. Unit.

2. **Injectio Hepatis, U. S. P.**—Liver Injection contains not more than 15 U. S. P. Units (injectable) in each c. c. *Average Dose, U. S. P.*—One U. S. P. Unit.

PHARMACOLOGY AND THERAPEUTICS

Liver furnishes a material which acts as a specific in the treatment of different types of hyperchromic macrocytic anaemia, *e. g.* pernicious anaemia. It supplies a substance which acting on the bone marrow brings about maturation of the red cells and which substance is missing or not available in this disease. In pernicious anaemia the hydrochloric acid becomes deficient and there is gastro-intestinal stasis, and it is possible that constant absorption of toxins prevents the formation of this substance. The anti-anaemic factor is produced in the stomach (*see* p. 348) from the interaction of a gastric ferment (intrinsic factor of Castle or haemopoietin of Wilkinson), and an extrinsic factor formed by the protein as the result of gastric digestion. The anti-anaemic principle is essential for the proper maturation of the megaloblasts in the bone marrow into normoblasts and reticulocytes. The nature of the extrinsic factor is believed to be vitamin B_{12} and there is evidence to suggest that vitamin B_{12} and intrinsic factor may unite to form a complex possessing greater heat stability than that of intrinsic factor alone. The effective haemopoietic principle in the liver is probably a combination of factors with somewhat different action, and it is possible to isolate three chemical substances from liver which exert varying effects on haemopoiesis in animals and man and which, to obtain maximum effect in man, should be given together.*

Treatment of pernicious anaemia with liver is an example of replacement therapy, *i. e.* the store of anti-anaemic factor in the liver of animals is utilised to supply the deficiency or absence of this principle. The value of liver treatment is well established in (*a*) *tropical*

* *Jour. Amer. Chem. Soc.* 1936.

megalocytic hyperchromic anaemia, which may be due to lack of the extrinsic factor in the diet and defective absorption from the intestine. It is possible that a similar condition exists in pellagra ; (*b*) *Addisonian pernicious anaemia* ; (*c*) *tropical sprue* ; *pernicious anaemia of pregnancy* ; and (*e*) *megalocytic hyperchromic anaemia* associated with infestation of the intestine with some parasites, lesions of the gastro-intestinal tract, and disease of the liver. All these anaemias have certain morphological features in common, they are megalocytic and hyperchromic, and the bone marrow shows hyperplasia of the more primitive red cells. The first sign of improvement after administration of liver is an increase in the number of recticulocytes within 7 to 12 days (*reticulocyte response or crisis*) reaching its maximum, *i. e.* about 15 to 20 per cent. of the total red blood corpuscle in about ten to fourteen days with oral therapy and between the third and seventh day with parenteral therapy. This indicates general improvement and both the red cell count and haemoglobin show a tendency to rise. The reticulocytes however decline in number but the red cells and haemoglobin continue to rise and within a few weeks the blood count becomes normal. The degree of the increase of reticulocytes is inversely proportional to the severity of anaemia and failure to attain this reticulocyte crisis after administration of some potent liver extract parenterally suggests that the case is not one of pernicious anaemia.

Along with the increase of red blood cells certain abnormalities of blood disappear and cells having normal size and shape gradually replace these. The general condition improves, the appetite returns, and weakness and depression disappear rapidly and the patient feels stronger.

Subacute combined degeneration of the spinal cord which is associated with pernicious anaemia also improves under liver extract but requires more intensive treatment by the parenteral route. It is possible that the neuropoietic factor of the stomach and haemopoietin of the liver act conjointly and is responsible for this improvement and highly purified and protein-free extracts are not as effective for the nervous system as the liver which has been less highly purified.

Its use has been advocated in **agranulocytosis** on the basis that leucopenia following administration of sulpha-group of drugs in animals improved with liver extract and folic acid.

Liver extract has also been found useful in **microcytic anaemia,** but its action in this type of anaemia is distinct from that in pernicious anaemia. This action is possibly due to the fact that liver not only contains iron but has a

high copper content. It has been found that the substance which cures secondary anaemia is not destroyed by ashing and that the ash of liver is as effective as the liver itself. Fractioning of this ash showed that the copper fraction was responsible for the cure.

Liver extract has been used to counteract certain unpleasant toxic effects which follow the administration of arsenic and bismuth, and it has been used in the dermatitis which follows the use of these drugs.

Prolonged administration of liver has been advocated in haemophilia on the theory that by forming fibrinogen it plays an important part in the production of those factors essential for coagulation of blood.

Liver is rich in vitamins specially vitamin B complex.

Mode of administration.—For therapeutic purposes the liver of sheep, goat, oxen and calf is used, and may be given either in the dry form or as liquid extract, or cooked according to the taste and choice of the patient, but prolonged cooking should be avoided. Half a pound daily of cooked liver is sufficient to bring about a prompt response. One ounce of the liquid extract is equivalent to half a pound of the fresh liver. But there are obvious disadvantages of using daily large amounts of liver which the patient very soon begins to dislike or may be unable to tolerate owing to gastro-intestinal disturbance. To obviate these difficulties liver extract may be used. Ordinarily administration by the mouth is sufficient, but in cases of severe relapse or when rapid action is necessary, the intramuscular or the intravenous route may be adopted. Experience has shown that parenteral administration intramuscularly is more efficacious and economical than the oral use. Although the greatest benefit is derived from intravenous method of administration, the general use by this route has potential dangers, and the routine method should be by the mouth, or by intramuscular injection. The dose for intravenous use is 0.1 grm. per kilo of body weight dissolved in physiological salt solution, so that 20 mils should contain 1 grm. of liver. It is necessary that the active principle should be sufficiently purified to avoid any allergic phenomena or a fall of blood pressure.

Untoward effects.—Injection of liver extract is sometimes followed by certain reactions. They are classified as follows: pain and local reaction ; acute fall of blood pressure ; and allergic manifestations such as urticaria, typical asthmatic attacks, collapse, dyspnoea, and generalised erythema. These are relieved by injection of adrenaline solution.

Proteolysed Liver Extract.—When the liver substance is subjected to the action of proteolytic enzymes, a better liberation of the active substance occurs. It is produced in fine granular powder for oral administration which is taken in hot milk in doses of 1 oz. daily. It is more palatable than ordinary liquid extract. Proteolysed liver extract for parenteral use is also available which is equal in potency to the best high-grade concentrates.

Liver with Stomach, U.S.P.—It is a brownish powder resulting from mixing a concentrated water solution of mammalian liver with minced fresh hog stomach tissue. **Dose.—1 U.S.P. Unit.**

Walden and Clowes have shown that this combination has greater potency, possibly three to four times than liver alone. It is used in the form of **Extralin,** which is available in capsules. 3 to 4 capsules are taken at a time three times a day with meals.

Ventriculus Desiccatus, B.P.C.—Desiccated Stomach. **Syn.**—Ventriculin; Gaster Sicca.

Source.—Whole desiccated stomach of hog, sheep or oxen, defatted with petroleum benzene. No taste, and very little odour.

Dose.—1/4 to 1 oz. or 8 to 30 grms.

Action and Uses

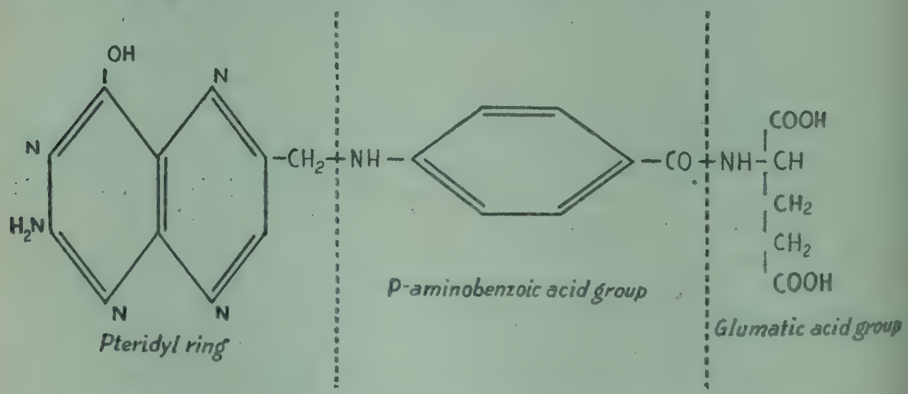
Castle and Townsend have shown that healthy stomach secretes a substance which when absorbed acts upon the bone marrow in such a way as to bring about maturation of the red blood cells. This is supposed to be stored either in the liver, kidneys or other organs. This antianaemic factor is produced by the action of an intrinsic factor which is probably an enzyme, present in normal gastric juice upon an extrinsic factor present in meat, yeast, etc. Patients suffering from pernicious anaemia do not secrete this anti-anaemic substance. Subsequently Isaac and Sturgis have shown that desiccated and defatted chopped up gastric tissue contains in abundance this active substance. Desiccated stomach therefore has been used in the treatment of **macrocytic hyperchromic anaemias**, *i.e.* pernicious anaemia, haemolytic anaemias, and cases intolerant to liver. The usual dose is 15 grm. of the dried material corresponding to 100 grm. of the fresh stomach which is equivalent in effect to 300 grm. of fresh liver. Safe clinical dose is 10 grm. for each million red cell deficit in the count. When the blood returns to normal it should be continued in 10 grm. doses four to five times a week. It is of special value in preventing and treatment of symptoms due to **subacute combined degeneration** of the spinal cord. The best form of administration is in some fruit juice or milk but not in hot fluids.

FOLIC ACID

(Not official)

Syn.—Pteroylglutamic Acid.

It will be observed from the structural formula that folic acid consists of (*a*) glutamic acid, (*b*) *para*-amino-benzoic acid, and (*c*) pteridyl ring.



Folic acid is a constituent of vitamin-B complex. It is present in minute quantities in normal food and also in the body in conjugated form, and in this form it cannot be utilised until free folic acid is liberated by bacterial action. It has been suggested that folic acid is the fundamental substance essential to the normal metabolism of the cells of the bone marrow.

It has been observed that if young rhesus monkeys were kept on a diet of casein, polished rice, whole wheat, salt mixture, cod-liver oil and ascorbic acid, a syndrome (sprue syndrome) developed characterised by anaemia, leucopenia, loss of weight, diarrhoea and ulceration of the gum ; and the animals died in 26 to 100 days. Addition of riboflavin, nicotinic acid or thiamine, separately or in combination did not prevent death. But addition of Brewer's yeast (10 grm.) or liver extract (2 grm.) promoted and maintained normal growth and normal blood picture. It was supposed that yeast and liver extract contained some vital nutritional element which was termed *vitamin-M* because its deficiency in monkeys caused retardation of growth, anorexia and leucopenia. Subsequently, a substance was extracted from liver extract, yeast and spinach which was found to be essential for the growth of *Lactobacillus casei* (designated as *L. casei factor*), and for the growth of *Streptococcus lactis R* (*Str. faecalis*), curative of vitamin-M deficiency in monkeys and necessary for normal growth and haemoglobin formation in chicks. Later, a crystalline folic acid was synthesised which was identical with L. casei factor.

Folic acid has been found useful in **macrocytic anaemia** with megaloblastic changes in the bone marrow. These include Addisonian pernicious anaemia, nutritional macrocytic anaemia, anaemia of pregnancy, pellagra, sprue and idiopathic steatorrhoea. In these conditions its use produces a complete haematological response and correction of megaloblastic dysplasia of the bone marrow. It is possible that folic acid may replace liver extract specially in those cases who show allergic reaction. It has no effect in microcytic **hypochromic anaemia.**

Peripheral neuritis and subacute combined degeneration of the spinal cord do not improve under folic acid. On the other hand complications may arise during treatment even though there may be good haematological response. Folic acid therefore should be regarded as an adjunct to liver therapy and not a complete substitute for it.

It has been observed that administration of minute quantities of succinylsulphathiazole prevents synthesis of folic acid. Sulphonamides compete with p-aminobenzoic acid for the enzyme normally necessary for the building up of folic acid necessary for the formation of granulocytes. Folic acid therefore is used in the treatment of **agranulocytosis.** Its use has also been suggested in **leucopenia** on the idea that leucopenia ordinarily following the administration of certain drugs in experimental animals could be prevented by folic acid.

Dose.—Minimum therapeutic dose is 5 to 15 mg. (1/12 to 1/4 gr.) daily, by the mouth or parenterally. Ordinarily 2.5 to 5 mg.

(1/24 to 1/12 gr.) daily is sufficient. It may be used in larger dose 100 to 150 mg. ($1\frac{1}{2}$ to $2\frac{1}{2}$ grs.) daily by mouth, or 75 to 150 m parenterally, daily. Maintenance dose is 25 mg. (2/5 gr.) orall or 20 mg. (1/3 gr.) by intramuscular injection weekly.

VITAMIN B_{12}

(Not official)

Syn.—Rubramin; Anacobin.

Isolation of Vitamin B_{12}, a red crystalline compoun from liver as a potent anti-pernicious anaemia factor a great achievement within recent years. This substan is essential for the growth of *Lactobacillus lactis* Dorn and is called the **LLD factor.**

The definite chemical constitution of vitamin B_{12} not known, but it contains an element of cobalt, whic has been shown to play a role in iron deficiency anaemia i man. The source of this new compound is liver sever tons of which yielding only a few grammes. A simila compound has been isolated from cultures of *Streptomyc griseus*, the organism which produces streptomycin, an which is identical with vitamin B_{12} derived from liver a least so far as its haematological response is concerned.

Vitamin B_{12} is almost specific against **perniciou** (Addisonian) **anaemia.** Within a few days the patien feels stronger, becomes mentally more alert, appetite im proves and gains in weight. It is not as effective agains other types of megaloblastic anaemias of pregnancy an sprue where folic acid is more effective.

The great advantage of vitamin B_{12} over ordinar liver extract is that it relieves or at least arrests th **neurological disturbances** (combined degeneration of th spinal cord) usually present in pernicious anaemia. Ho it attains this neurological cure is not definitely know possibly because of the fact that large amount of anti anaemic factor in the form of vitamin B_{12} can be adminis tered during a short period without any untoward effec Moreover no untoward reaction follows as is sometime observed with liver extract. In this treatment a suggeste schedule is 10 micrograms of vitamin B_{12} injected intra muscularly daily or on alternate days for 3-6 month or alternatively 40 mcgrm. weekly for first six months an half the amount thereafter and the dose increased on th least sign of relapse.

Folic acid has been shown to act as a synergist t liver extract and vitamin B_{12} and preparations containin vitamin B_{12} 25 mcgrm. and folic acid 3 mg. in capsule for oral administration once daily have been recommende as a maintenance dose in patients suffering from perniciou anaemia.

The **dosage** of vitamin B_{12} is calculated in mcgrm. t

be administered parenterally. Initial dose is 40 to 80 mcgrm., followed by 20 mcgrm. weekly for three months, and 30 mcgrm. every three weeks afterwards. Effective oral dose is 30 to 60 times that of the parenteral dose.

Standardization of dosage.—For the antipernicious anaemia factor, the only available test until recently was the assay on clinical cases which was neither consistent nor reliable. It is considered more rational to express the dosage of liver extracts and other concentrates of antipernicious anaemia factor in accurate and logical terms. It has been found that potent liver extracts contain a factor (vitamin B_{12}) necessary for the growth of an organism, *Lactobacillus lactis* Dorner. This LLD factor is present in an almost direct proportion to the potency of the liver extracts used in the treatment of pernicious anaemia. The previous methods of stating dosages as the number of millilitres of a liver extract or milligrams of crude solids administered or in "liver equivalents" or the weight of liver from which the dose is prepared, are misleading on account of variations in the potency of original liver, variable yields in the course of extraction and purification and differences in the extent of purification as between one liver extract and another. The microbiological assay method using crystalline vitamin B_{12} as a standard now permits standardization in terms of vitamin B_{12} activity.

Class B : **Drugs used in Microcytic Hypochromic Anaemia**

FERRUM

Iron. (Ferr.)

Syn. I.V.—*Loha*, Beng. Hind.

Source.—Iron in the form of fine bright wire having a diameter of about 0.1 millimetre.

Official Preparation

1. **Syrupus Ferri Phosphatis Compositus.** *Syn.—Parrish's Food ; Parrish's Syrup ; Chemical Food.*—1 1/8 grs. ferrous phosphate, or 1/2 gr. iron, 1 3/4 grs. tricalcium phosphate in 120 ms. **B. P. Dose.—30 to 120 ms. or 2 to 8 mils.**

Iron salts group themselves into three classes :—(1) Ferrous or Protosalts based upon Ferrous Oxide FeO ; (2) Ferric or Persalts upon Ferric Oxide Fe_2O_3 ; and (3) Scale Preparations. Ferrous salts soon become ferric from the absorption of atmospheric oxygen, especially in the presence of oxidising agents, as chlorine, nitric acid, etc.

1. Ferrous Salts

Ferri Sulphas. (Ferr. Sulph.). $FeSO_4,7H_2O$. Syn. I. V.—*Hirakas*, Beng. *Hira kasus*, Hind.

Source.—Ferrous Sulphate, is prepared by the action of diluted sulphuric acid upon iron.

Characters.—Transparent green crystals ; or a pale bluish green crystalline powder ; metallic, astringent taste. *Soluble* in about 1.5 parts of water ; insoluble in alcohol (90 p. c.). Contains 1 gr. of iron in 5 grs.

B. P. Dose.—3 to 5 grs. or 0.2 to 0.3 grm.

Official Preparations

1. **Ferri Sulphas Exsiccatus.**—Ferrous sulphate deprived of part of its water of crystallisation by drying at a temperature of 40°C. Contains not less than 77 p.c. $FeSO_4$. 3 grs. contain about 1 gr. of iron. A greyish-white powder, slowly but completely soluble in boiled and cooled water. **B. P. Dose.—1 to 3 grs. or 60 to 200 mg.**
2. **Pilula Ferri Carbonatis.** *Syn.—Blaud's Pill : Pilula Ferri.*—20 p. c. ferrous carbonate, or 3 grs. of iron in 30 grs. **B. P. Dose.—5 to 30 grs. or 0.3 to 2 grms.**

Ferri Carbonas Saccharatus. (Ferr. Carb. Sacch.).—Saccharated Iron Carbonate.

Source.—Saccharated iron carbonate is ferrous carbonate, wh may be partly oxidised, mixed with glucose. Contains ferrous s phate 1000 G., liquid glucose 307 G., sodium carbonate 1078 water q.s. Contains not less than 50 p.c. ferrous carbonate 7½ grs. iron in 30 grs.

Characters.—An olive-brown, slightly hygroscopic powder ; taste, feebly ch beate. Partially *soluble* in water, soluble with effervescence in dilute hydrochl acid.

Incompatibles.—Vegetable astringents, acids and acid salts.

B. P. Dose.—10 to 30 grs. or 0.6 to 2 grms.

2. Ferric Salts

Liquor Ferri Perchloridi. (Liq. Ferr. Perchlor.).—Solution Ferric Chloride is an aqueous solution containing 15 p.c. w/v $FeCl_3$, or about 2½ grs. of ferric chloride or 4/5 gr. of iron in 15 m

B. P. Dose.—5 to 15 ms. or 0.3 to 1 mil.

Non-official Preparation

1. **Liquor Ferri et Ammonii Acetatis.** *Syn.—Basham's Mixture.*—Tinct. fe perchlor. 4 ; acid acetic. dil. 6 ; liquor ammon. acetatis 50 ; aromatic elixir 1 glycerin 12 ; water *q. s.* to 100. *Dose.*—1/2 oz. or 15 mils.

3. Scale Preparations

Ferri et Ammonii Citras. (Ferr. et Ammon. Cit.).—Iron a Ammonium Citrate is a complex ammonium ferric citrate. Contai 20.5 to 22.5 p. c. Fe, or about 9 grs. iron in 45 grs.

Characters.—Thin, dark-red, transparent scales ; taste, astringent, deliquesce in moist air. *Soluble* in 0.5 part of water ; feebly acid ; almost insoluble in al hol (90 p. c.).

B.P. Dose.—15 to 45 grs. or 1 to 3 grm.

Additional Non-official Preparations and Derivatives of Iron

1. **Syrupus Ferri Iodidi, B.P.C.**—Contains 7½ grs. of ferrous iodide or 1½ g of iron in 120 ms. *Dose.*—30 to 120 ms. or 2 to 8 mils.
2. **Syrupus Ferri Phosphatis cum Quinina et Strychnina, B.P.C.** *Syn.—Easto Syrup.*—Contains 1 gr. ferrous phosphate, or 1/2 gr. iron, 4/5 gr. quinine sulpha 1/60 gr. strychnin. hydrochlor. in 60 ms. *Dose.*—30 to 60 ms. or 2 to 4 mils.
3. **Ferri et Quininae Citras, B.P.C.**—Thin, greenish-yellow scales of a bitt taste. Soluble in 0.5 part of water. Contains 14.5 to 15.5 p.c. anhydrous quinine, a 12 to 14 p. c. iron ; or 2 grs. iron and 2½ grs. quinine in 15 grs. *Dose.*—5 to grs. or 0.3 to 1 grm.
4. **Ferri et Potassii Tartras.** *Syn.—Ferrum Tartaratum.*—In transpare garnet coloured scales. Soluble in water. *Dose.*—5 to 10 grs. or 0.3 to 0.6 grm
5. **Ferri Lactas, B.P.C.**—In greenish-white crystals, soluble 1 in 40 of wat Readily assimilated. One of the least astringent forms of iron. *Dose.*—2 to 10 g or 0.12 to 0.6 grm.
6. **Liquor Ferri Hypophosphitis, B. P. C.**—Solution of ferric sulph. 14.2 solution of ammonia 23 ; citric acid 7.60 ; sodium hypophosph. 9.60 ; sod. citr 6.60 ; water q. s., stronger chloroform water to 100. *Dose.*—10 to 30 ms. or to 2 mils.

Pharmacology

Externally.—Iron salts have no action on the un broken skin, and are not absorbed by it. A solution o ferric salts when applied to a denuded surface, mucou membrane, sores or ulcers coagulates the albuminou secretion, as well as the albumin of the tissues. It als coagulates blood and plasma. The circulation of the par is greatly reduced by the compression of the coagulate protein from outside and not by the contraction of th muscular fibres of the walls of the blood-vessels. If ther is any haemorrhage, it is readily arrested by (1) the com

pression of the blood-vessels from without, and (2) the plugging of the bleeding vessels by the clotting of the blood within them. Therefore it is a powerful **styptic.** It acts as an astringent or irritant according to the concentration used ; the irritant effect being due to the acid ion and not to the metal. Iron however has no specific poisonous action on living matter like mercury or antimony. The perchloride, the pernitrate and the persulphate of iron are all strong local astringents. Ferrous and organic salts are feebly astringent.

Internally. **Mouth.**—Iron blackens the teeth and the tongue, from the deposition of iron tannate or sulphide. This is supposed to be due to tannic acid of the food precipitating black tannate of iron, or to the sulphide of iron formed by the action of hydrogen sulphide present in carious tooth. It has a styptic taste, and the ferric salts have a similar action here as on the raw skin.

Stomach.—All iron preparations, in whatever form they are taken by the mouth, are mostly converted into chlorides in the stomach, and by precipitating the proteins of the food and the superficial cells of the mucous membrane act as astringent. Even an albuminate is decomposed into a chloride. If given in large doses, or if continued for a long time, all iron salts set up irritation and indigestion with pain, nausea and vomiting. In the presence of gastric secretion and easily oxidisable substances, ferric ions are reduced to ferrous. In fact all iron salts are transformed into simple ferrous compounds before they are absorbed by the duodenum and upper part of the intestine ; an acid condition of the duodenum favours absorption while alkalinity retards it. This is why iron salts are absorbed from the duodenum and upper part of the jejunum where the reaction is acid. The scale preparations however do not ionise in the stomach and therefore do not impair digestion and do not act as astringent.

Intestine.—In the lower part of the intestine the ferrous compounds coming in contact with alkaline secretions are converted into insoluble phosphates, carbonates or other complex salts which are not so easily absorbed, the unabsorbed portion continues to exert its astringent action and produces constipation, which lower down is converted into sulphides and tannates by the sulphuretted hydrogen and tannic acid, the latter being derived from the vegetable food, and are passed out with the faeces which are coloured black.

Absorption and metabolism.—Normally iron balance is maintained by regulation of absorption according to the body requirements rather than by excretion of unwanted iron. Absorption of iron is great when the body needs it, as after haemorrhage or in iron deficiency anaemia, and

almost negligible when the body is fully stocked with iro Thus Balfour et al.* have shown that normal individua absorb very little of a test dose of radioactive iron. th polycythaemic patients absorb no more than a trace, whil persons with iron-deficiency anaemia absorb ten times much. Sufficient iron to balance daily excretion is ord narily derived from the food taken.

Iron can only be absorbed in ionic form as exists the inorganic salts. In the organic compounds the met exists in the non-ionisable state ; while in the variou double salts containing citric and tartaric acids, the ir though exists in the non-ionisable form is easily di sociated. The ferric salts readily form insoluble com pounds with a number of amino-acids, with phosphoru containing substances as nucleic acid, and with phyt acid. The food iron exists in both inorganic and organ form. The former is readily available for absorption, th latter, chiefly in the form of porphyrin compounds, mus be broken down before ionic iron is liberated.

The factors which influence iron absorption are (a the state of saturation of body stores ; (*b*) the reactio of the medium in which the ionic iron is in solution ; an (*c*) the form in which iron is presented, *i. e.* the ionic forn and the valency of the iron available for absorption. Thu iron salts are poorly dissociated in a solution with a pl greater than 5.0. Hence maximum absorption takes plac in the stomach and upper part of the small intestine wher the reaction is favourable. None at all is absorbed fron the colon. All iron salts are absorbed as ferrous ions b the intestinal epithelium by way of the blood, but dis appears rapidly from the circulation to be stored in th liver and to a less extent in the spleen and kidneys.

Dietary factors including traces of other metals ar intimately related to the absorption and utilisation of iron The vitamin content is of great importance. As men tioned before ascorbic acid reduces ferric compounds t ferrous *in vivo* as well as *in vitro* and helps absorption whilst vitamin D helps haemoglobin formation and iro storage. On the other hand an excess of phytic aci present in wholemeal bread may interfere with absorptio of iron. This disadvantage is overcome by fortifying th loaf with calcium which reduces the formation of insolub iron phosphate. Absorption of iron into the blood strean is direct, and a rise in the iron content of the plasma is no preceded by a rise in the iron content of the lymph of th thoracic duct. After absorption both the divalent an trivalent iron ions are stored in the body as the iron-con

* *Jour. Exp. Med.* 1942, 76, 15.

taining protein known as *ferritin*, found abundantly in the liver, spleen, bone-marrow as also in the cells of the intestinal mucosa when its absorption is proceeding.

It has been possible to follow the distribution of iron in the body by the administration of radioactive isotopes of iron. (Fe_{59} prepared by bombarding ordinary iron, Fe_{58}). Under normal conditions very little of the iron reaches the red blood cells, but when iron reserves and haemoglobin are depleted, it is absorbed in abundance.

Recently the idea has been put forward that the formation of haemoglobin by iron is helped by the presence of minute quantities of copper which acts as a catalytic agent and assists in the conversion of inorganic iron into haemoglobin thus accelerates the process of red cell formation. Moreover a copper-free iron salt fails to improve induced anaemia of rats. It has been estimated that the blood of man contains on an average 0.132 mg. of copper per litre, of which 50 p.c. exists in haemoglobin. Enough copper is found in almost any diet to supply all the haemopoietic needs of adults. There is no evidence that copper is effective in preventing or treating anaemia unless the supply of iron is sufficient. In conjunction with copper manganese enhances the catalytic action of copper.

Blood.—Iron is an essential constituent of every cell in the body and the normal process of cell oxidation depends upon its presence. About two-thirds of the iron in the body exists in the form of haemoglobin. Its production therefore is intimately associated with iron metabolism. It exists in the body as (*a*) *plasma iron*, which represents mainly iron in transit from intestinal tract to the depot ; or from sites of haemoglobin breakdown to sites of storage ; or to bone marrow for synthesis of haemoglobin. The normal concentration of plasma iron is 50 to 180 mcgrm. per 100 mil ; (*b*) *combined with haemoglobin*, which represents 92 to 98 p.c. of the total ; (*c*) an *inactive degradation product*. An adult man contains about 3.0 to 3.5 grms. of iron, of which about 2.4 to 2.7 grms. are in the form of haemoglobin. About 20 mg. is excreted daily on a normal diet, and this loss is replaced by the iron of the food and a minimum of 6 to 12 mg. is required to maintain this equilibrium. The iron content in different foods varies however. In health iron has very little effect upon either the quantity or the quality of the blood-corpuscles but increases the reserve iron, so that its transformation into haemoglobin occurs only as required by the body ; but in anaemia both the number of corpuscles and their haemoglobin value are markedly increased by iron.

Conservation of Iron.—About 1 p.c. of the circulating red cells become effete every day and are removed from the circulation, but the iron liberated from the breakdown

of the haemoglobin is not excreted but very carefully preserved in the form of *haemosiderin granules* within the reticulo-endothelial cells and used for haemoglobin synthesis in preference to the iron present in the body stores. Similarly, iron used by injection into the circulation is utilised for haemoglobin synthesis before the reserves in the iron stores.*

Clearance.—Under normal conditions only minute quantity of iron is absorbed and excreted, and practically the entire amount of iron liberated by the breakdown of haemoglobin is retained in the body and utilised again for the formation of haemoglobin. The amount excreted by the urine is very small, 0.25 to 0.3 mg. daily, and it is generally believed that the largest amount is excreted through the bowels, mainly the wall of the colon, which normally contains 10 to 50 mg. daily, and this represents only that portion of food iron which has escaped absorption. It is generally believed that the iron content of the body is controlled through the regulation of absorption and not by excretion.

THERAPEUTICS

Externally.—Though iron salts are powerful astringents and styptics they are not much used nowadays as they cause a dirty coagulum and irritation of the tissues. The solution of perchloride mixed with equal quantity of glycerin is used as a paint for its astringent action in different conditions of the throat and tonsils, *viz.* enlarged tonsils, diphtheria and sore-throat. Ferrous sulphate or *copperas* has been used as a disinfectant for cesspits, water closets, etc. It acts by precipitating the proteins which mechanically carry down the bacteria.

Internally. **Gastro-intestinal tract.**—Because of the astringent effect on the intestine, iron salts specially the ferric compounds, are sometimes used in diarrhoea. It is specially useful in those cases where the patient is anaemic. Here it acts not only as an astringent but by improving the condition of the blood gives tone to the intestine. An enema of the solution of perchloride of iron (60 ms. in 1 pint of water) kills thread-worm.

Blood.—Iron is a valuable remedy in **anaemia.** The forms of anaemia which respond to iron treatment are those characterised by small size and pallor of the red cells, pallor or hypochromia due to deficient corpuscular content of iron and haemoglobin. Iron salts are therefore extensively used in chlorosis, scrofula, chronic nephritis, convalescence from acute and chronic illness, etc. Ferrous salts are the most potent preparations and most of the idiopathic microcytic anaemias are cured by these salts.

* Dubach et al. *Jour. Lab. Clin. Med.* 1946, 31, 1201.

Some cases are however refractory and do not respond to iron. This refractoriness is often due to deficient absorption from the intestine.

Anaemia and Chlorosis.—Ordinary forms of anaemia traceable to some definite cause such as scurvy, malaria, protracted haemorrhage, and lead poisoning, etc., are materially benefitted by a course of iron, as well as by removal of the cause.

Iron is the most valuable remedy in chlorosis. Although the actual amount of food iron is not deficient in this disease, chlorotic patients are not able to assimilate enough iron from the food ; moreover owing to poor appetite and digestion, the quantity becomes still less and the body soon becomes depleted of iron causing anaemia with deficiency of haemoglobin. There is therefore deficient supply of oxygen for the body requirements as evidenced by breathlessness, cardiac weakness and oedema. Iron by improving the condition of the haemoglobin brings on an improvement in the patient's condition.

In anaemia due to blood loss, recovery generally follows without any use of iron, as the reserve store of iron is called upon to replace this loss. But recovery is hastened by the administration of iron to increase the reserve store of iron. **Nutritional anaemia** of infants, **achlorhydric anaemia** due to deficient absorption of iron due to deficiency of hydrochloric acid, and **anaemia of pregnancy** due to increased demand of iron, improve with the administration of iron.

If the anaemia is due to malaria, ferri et quinin. citras, or Easton's syrup may be given with advantage. The same preparations may also be employed as a tonic during convalescence after an acute febrile attack or any other protracted illness.*

Splenic anaemia.—Davidson† has pointed out that although it is said that iron is of little value in this form of anaemia, it has given excellent result in this condition. He holds that the three common causes of hypochromic anaemia are frequently present in this condition, *viz.*—(*a*) defective intake of iron through poor diet ; (*b*) deficient absorption of iron from the presence of achlorhydria ; and (*c*) increased demand of iron from blood loss.

Pernicious anaemia.—Since pernicious anaemia arises from deficiency of the specific anti-anaemic factor contained in the liver, iron is of little value in this condition. Pernicious anaemia when treated with whole liver does not as a rule require iron as this organ is particularly rich

* Ferr. et quinin. cit.	grs. 10
Acid. hydrochlor. dil.	ms. 10
Liq. strych. hydrochlor.	ms. 8
Sp. chlorof.	ms. 15
Aqua	ad oz. 1

† *Lancet*, Sept. 1934.

in that metal. With the introduction of the parenteral method of treatment of this disease the position has changed, as the anti-anaemic fraction does not contain any iron which is given as injection and in consequence the body's reserve store of iron is rapidly utilised in order to supply the large requirement of the haemoglobin synthesis which occurs during recovery. And it has been found that there is a marked acceleration in the speed of recovery, both in the haemoglobin level and in the patient's physical condition by giving 60 to 90 grs. of iron and ammonium citrate daily.

Many conditions depending on anaemia, and which are sometimes more troublesome, are benefited by a course of iron. Thus amenorrhoea when due to anaemia often yields to iron specially when given in combination with aloes, as Blaud's pill and Pilulae aloes et ferri.. Similarly gastric catarrh and oedema so common in profound anaemia, also disappear with the exhibition of iron. These effects are due to improvement of haemoglobin which follows the use of iron and not to any special action either on the stomach or the circulation. Iron being an integral part of all cells of the body it is possible that it helps to perform their function better when there is an abundant supply of this element, therefore iron is a valuable tonic.

Bright's disease.—Acetate of iron is a valuable remedy in this disease. It not only improves the blood, but lessens or removes the albumin. Basham's mixture is a very useful preparation in chronic parenchymatous nephritis.

Scrofula and other tubercular affections are benefited by a course of iodide of iron.

Intravenous use of Iron.—Some patients with hypochromic anaemia do not improve with iron given orally, while others suffer from gastro-intestinal irritation so that adequate dosage cannot be given. These improve by intravenous administration. Slack and Wilkinson* have shown that Saccharated Oxide of Iron (**Ferrivenin** is a 2 per cent. solution) can be administered intravenously in the treatment of iron deficiency anaemia, and is safe, effective and produces mild reaction, if any. It is administered in doses of 25 mg. 1st day; 50 mg. the 2nd day; 100 mg. on 3rd day; and 200 mg. on the 4th day and on subsequent days. May be administered twice a day at six hourly interval, if necessary. It should be diluted with 5 to 10 mils of sterile water and administered very slowly taking one minute for each mil.

Prescribing hints.—It is now generally recognised that ferrous salts are more efficacious than ferric, and that much larger doses than formerly are required to get the optimal effect. It is also realised that parenteral administration of iron is seldom necessary. The organic salts are non-astringent, but they have not proved so effective as the inorganic ones, as the larger molecules have to be broken down by the digestive juices before they are absorbed. All iron preparations are best given after meals. Insoluble preparations being less irritating to the stomach are tolerated better, therefore Blaud's pill and saccharated iron are largely used, the latter pre-

* Lancet, Jan. 1, 1949.

paration being very useful for children. The scale preparations may be used in the form of mixture with equally good result. Constipation often gives trouble though it is less with ferrous salts which are less astringent. When given in pill, combine with aloe and belladonna, and magnesium sulphate when prescribed in the form of a mixture.

When given in a mixture, glycerin or lemon juice covers the ferruginous taste. The infusion of quassia, calumba or chiretta may be used as a vehicle as they do not contain tannin. The inky colour which results if they are combined with cinchona or digitalis, is cleared by the addition of a few drops of diluted phosphoric acid. The action of iron is not affected by this chemical change. By addition of alkali the acid reaction of the iron salts and their astringency are lessened, and therefore Blaud's pill is so well-borne. Syrupus Ferri Phosphatis and Syrupus Ferri Iodidi should be given alone diluted. When prescribed with acids, Syr. Ferr. Iod. liberates iodine and with alkalies will throw down insoluble iron compounds. To prevent blackening of the teeth, iron mixture should be swallowed through a glass tube or a quill. Parrish's chemical food is an excellent preparation for children and delicate women. Citrate of iron and quinine should not be mixed with alkalies or alkaline carbonates as the quinine is precipitated.

CLASS C : Drugs altering the coagulability of the blood

One of the most important functions of the blood is its power to coagulate shortly (generally between 3 to 5 minutes) after it leaves the blood vessels. The essential part of the clot is fibrin, an insoluble protein compound not normally present in the circulating blood, but formed from fibrinogen present in the plasma by the action of thrombin. In the circulating blood thrombin exists as inactive prothrombin which is changed to thrombin by the addition of tissue extracts, which contain lipoid thromboplastic substances (thromboplastin, thrombokinase, cephaline) ; possibly by a similar substance liberated from the disintegration of blood platelets after haemorrhage ; and by the presence of minute amounts of ionised calcium salts. The formation of prothrombin depends upon vitamin K, and interference with its absorption, as happens in jaundice, decreases prothrombin content of the blood with delayed coagulation.

1. Drugs increasing the coagulability of the blood (Coagulants)

Coagulation of blood can be increased therapeutically by the administration of calcium salts ; transfusion of whole blood not only to replace the lost blood but also to supply any elements that may be lacking ; normal serum, which contains some thrombin and thromboplastin : human fibrin foam, human fibrinogen and human thrombin ; by congo red and snake venom ; and vitamin K.

HUMAN FIBRIN FOAM, B. P.

Human Fibrin Foam is a dry artificial sponge of human fibrin. A fine white sponge of firm texture. Insoluble in water.

Storage.—Should be kept in sterile container, sealed so as to exclude micro-organisms, protected from light and stored in a cool place.

HUMAN FIBRINOGEN, B. P.

Human Fibrinogen is a dried preparation of the soluble constituent of liquid human plasma, which, on the addition of thrombin, is transformed to fibrin. White powder or friable solid. Readily soluble in 0.9 p.c. w/v solution of sodium chloride in water to form a colourless solution, which may clot spontaneously on standing.

Storage.—Should be kept in a sealed container and stored in a cool place, protected from light.

Labelling.—Should state (1) the amount contained in the container, and (2) that the substance should be used as soon as possible after reconstitution.

HUMAN THROMBIN, B. P.

Human Thrombin is the enzyme which converts human fibrinogen into fibrin. A cream-coloured powder. Readily soluble in a 0.9 p.c. w/v solution of sodium chloride in water, forming a pale yellow solution.

Storage.—Same as other preparations.

Labelling.—Should state (1) the number of clotting doses contained in it, (2) conditions under which the preparation should be stored, (3) the date after which the preparation is not intended to be used.

ACTION AND USES

Human fibrin foam is used, in conjunction with human thrombin, as a valuable haemostatic agent in brain and lung surgery. A piece of the foam is saturated with a solution of human thrombin in injection of sodium chloride and placed in contact with the oozing surface. Blood comes into intimate contact with the human thrombin in the interstices of the foam and coagulates immediately.

Human fibrin film is used in brain surgery for the repair of peripheral nerves ; it is specially suited for application to burns and skin graft lesions. Both human fibrin foam and fibrin film are also harmless when left in situ.

Human fibrinogen is largely used in conjunction with human thrombin, for the promotion of fibrin clots in certain surgical procedures. Its great advantage is that when introduced into the body and left in situ, it does not produce any undesirable reactions. Along with human thrombin, it has also been used for the surface treatment of burns, for nerve suturing, skin grafting and in coagulum pyelolithotomy.

Human fibrinogen also contains a globulin with the property of reducing the clotting times of haemophilic patients and a dose of 10 mil of a 2 per cent. solution in injection of sodium chloride given intravenously usually maintains the reduced clotting time for 24 to 36 hours. It is usually used to prevent or arrest severe bleeding when the haemophiliacs are subjected to surgical intervention.

Human thrombin is used, in conjunction with human fibrinogen or fibrin foam, as a local haemostatic agent in various surgical procedures.

Congo Red.—A reddish brown powder, soluble in water. Used intravenously in the treatment of internal haemorrhages, specially haemoptysis, and as a diagnostic agent in amyloid disease. It increases the number of monocytes, fibrin and blood platelets and induces thrombocytosis, and causes a reduction of clotting time.

Dose.—5 to 10 mils or 75 to 150 ms. of 1 p.c. solution *intravenously*, repeated after 4 to 6 hours ; or 0.25 mil of 1 p.c. solution per kg. body weight.

Snake Venom.—The venom which increases coagulability of the blood and therefore stops bleeding is that of Russell's Viper Venom. which may be applied whenever the bleeding point is accessible.

Moccasin Venom given subcutaneously or intradermally decreases the permeability of capillaries and stops remote haemorrhage, but not in haemophilia. *Dose.*—5 to 15 ms. (0.3 to 1 mil) of 1 in 3000 solution.

2. Drugs diminishing the coagulability of the blood (Anticoagulants)

Coagulating power of the blood is diminished by inactivating the calcium by citrates, oxalates or fluorides. But these are useful only to prevent blood from clotting outside the body, as for instance, for determination of blood cholesterol or in the preparation of blood for transfusion, when Injectio Sodii Citratis Anticoagulans is used. Oxalates and fluorides are too poisonous to be used in blood transfusion. All these substances act by removal of free ionised calcium. Citrates when given by the mouth has no effect on clotting as they are converted into carbonates in the tissues (*see* page 79). Anticoagulants which act in the living body are heparin, leech extract and dicoumarol. Leech extract or hirudin contains an anticoagulant substance which prevents clotting. Similarly, heparin obtained from liver increases the antithrombin of the blood.

Hirudin.—It is largely used in laboratory experiments ; gr. 1/3 will keep 1000 mils of blood in a fluid condition for a considerable time. It has been used as an anticoagulant in blood transfusion. The dose being 20 to 300 mg (1/3 to 5 grs.) in 50 mils of normal saline.

HEPARINUM. (Heparin.).—Heparin is a sterile preparation containing the sodium salt of a complex organic acid present in mammalian tissues, and having the characteristic property of delaying clotting of shed blood. It contains not less than 75 Units per mg.

Characters.—A greyish-brown powder. Moderately hygroscopic. Completely *soluble* in water, and in saline solution, forming a clear, colourless or straw coloured liquid.

B. P. Dose.—By intravenous injection :—6000 to 12,000 Units.

Official Preparation

1. **Injectio Heparini.**—A clear, colourless or straw coloured liquid free from turbidity and from matter which deposits on standing. **B. P. Dose.**—6000 to 12,000 Units by intravenous injection.

Action and Uses

Heparin contains chondroitin, a nitrogenous carbohy-

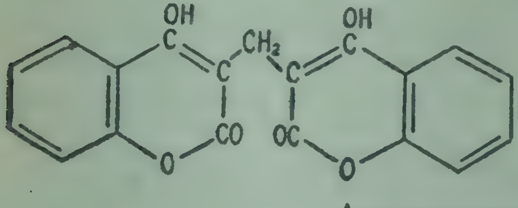
drate derivative with several molecules of sulphuric acid. It is a powerful **anticoagulant** and acts by preventing conversion of prothrombin into thrombin or by neutralising the action of thrombin itself. 1 mg. of purified heparin may prevent the coagulation of 500 c.c. of cat's blood at 0°C. for 24 hours. It is inactive when given by the mouth. Pure preparations are non-toxic and are used intravenously without any changes in the respiration, blood-pressure, temperature and blood chemistry.

Because of its anticoagulant effect heparin is chiefly used in blood **transfusion.** Its addition to drawn blood has no advantage over citrate although it may be used in the proportion of 1000 units for every 100 mils of blood withdrawn. It is generally introduced into a vein of the donor and blood withdrawn ten minutes later. It has been used in the treatment of **coronary** and **cerebral thrombosis.** It is employed specially as a precaution against **post-operative thrombosis** and **embolism** by continuous administration alone or with dicoumarol exhibited by the mouth. It has been tried in bacterial endocarditis with simultaneous use of sulphapyridine by the mouth but the results were disappointing.

Heparin acts quickly and the effects disappear quickly so that it has to be administered every four hours to maintain the effect. It may be administered without laboratory control. On the other hand it is expensive.

Disadvantages.—Heparin neutralises serum complement, interfering with Wassermann reaction. It acts not only on thrombokinase but on other enzymes, and prevents their action. In larger concentration it acts on plasma proteins and thus interferes the sedimentation rates of red blood cells. *All these effects are instantly neutralised by Protamine*, which abolishes heparin effect. 5 to 10 mils of 1 per cent. protamine sulphate solution administered intravenously brings the coagulation time to normal.

DICOUMAROL. Syn.—Dicoumarin.—Dicoumarol is 3 : 3′-methylene-bis-4-hydroxycoumarin.



Characters.—A white or creamy-white, microcrystalline powder ; odour, slight but pleasant ; taste, slightly bitter. Slightly *soluble* in water ; readily soluble in strong solution of alkalies.

B. P. Dose.—3/4 to 5 grs. or 50 to 300 mg. daily.

Action and Uses

The part played by prothrombin in the coagulation of the blood has been discussed. Dicoumarol when administered by the mouth or the sodium salt, intravenously, acts as a powerful anti-coagulant by lowering the prothrombin content of the blood plasma. It takes about 32 to 48 hours to produce the effect, and thereafter, for a period of some days, depending on the dose, there is steady rise in pro-

thrombin time and the coagulation time. This effect lasts for several days after it is discontinued.

How it acts as an anticoagulant is not clear, although there are three possibilities : (*a*) inhibition of the formation of prothrombin in the liver ; (*b*) by helping its destruction ; and (*c*) suppressing its activity. Since it has no effect on the clotting of drawn blood its destruction is improbable. It possibly acts by interfering with the formation of vitamin K essential for prothrombin formation. It has no effect on the liver function, blood cells, blood urea, or on icteric index.

Dicoumarol therefore is used in all conditions where anticoagulant effect is indicated. It has been used for the prevention of **intravascular thrombosis** or to limit it when it has already formed. Similarly it has been used in **post-operative pulmonary embolism** and in gynaecological practice and in **post-partum thrombosis.** For prophylactic purposes it should be used for two mornings just prior to the operation in doses of 300 mg. (5 grs.), although some recommend its use on the day after the operation. It has also been used in phlebitis, coronary thrombosis and retinal thrombosis with success.

Advantage.—Dicoumarin is cheaper to prepare than heparin and can be given by mouth and also intravenously.

Disadvantage.—(*a*) Delayed action ; (*b*) effective dosage varies from case to case depending on the results of prothrombin estimation done either daily or every second day ; (*c*) haemorrhagic complications, specially haematuria frequently follow due not only to prothrombin reduction but also to action on the capillaries ; (*d*) effect on prothrombin level takes several days to disappear after stoppage of the drug ; (*e*) estimation of prothrombin demands great care which can only be done in a hospital with suitable laboratory facilities.

Contra-indications.—(1) Renal insufficiency, here response to dicoumarol is excessive ; (2) blood dyscrasias in which there is a tendency to bleed ; (3) prothrombin deficiency, *e.g.* in jaundice and severe disease of the liver ; (4) patients suffering from purpura ; (5) acute or subacute bacterial endocarditis, because of the tendency to bleed ; (6) high fever. Pyrexia increases susceptibility to dicoumarol action. Less difinite contra-indications are : (1) ulcers and open wounds ; (2) the imminence of surgical operation ; (3) gastric ulcer.*

Caution.—The *margin of safety* between effective therapeutic dose and toxic dose is very small and there is no easy way of standardizing the dosage in any individual patient. It is necessary to determine the prothrombin time daily for efficient and safe use. If the prothrombin time exceeds 80 to 100 p.c. of pre-treatment level **it should be taken as a danger signal.**

Overdosage.—The only danger of over-dosage is haemorrhage through excessive lowering of prothrombin level and thus lowering too far the coagulability of blood. The earliest symptoms are lassitude, malaise, severe aching of the region of the costo-vertebral joint, subcutaneous haemorrhage, ecchymosis, bleeding from the gums. *Treatment* consists in immediate transfusion of blood to

* *Lambert Rogers, Medical Annual,* 1944.

raise the prothrombin level. Its effect passes off quickly so that transfusion should be repeated several times. Although dicoumarol is antithrombin its effects are not antagonised by vitamin K. Davis and Margaret Porter* have however shown that when dicoumarol and vitamin K are administered simultaneously the coagulation-time curve rises more slowly and less steeply than when dicoumarol is given alone. They have further shown that where blood transfusion failed to produce any perceptible decrease in the prolonged prothombin time in which dicoumarol had induced haemorrhage, a second transfusion with vitamin K resulted in an immediate drop of the prothrombin and coagulation times to normal levels and that these normal values were maintained. The failure of vitamin K may be due to secondary changes produced by anaemia.

Class D : **Drugs used in certain blood diseases**

1. Drugs used in leukaemia and polycythaemia

Mustine (Nitrogen Mustard), Folic Acid Antagonists, Phenylhydrazine Hydrochloride, Radioactive Phosphorus (see page, 133).

MUSTINE. (Not official). **Syn.**—Nitrogen Mustard.—Nitrogen mustard is closely related as regards its chemical and physical properties to "mustard gas", which is not a gas but an oily liquid. It has assumed much clinical importance when it was discovered that at least two of the so-called "mustard gas", *viz.*, tris-(ß-chloroethyl) amine hydrochloride, $N(CH_2CH_2Cl)_3$ and methyl-*bis*-(ß-chloroethyl) amine hydrochloride, $CH_3N.(CH_2CH_2Cl)_2$ appeared to be of some value in the treatment of neoplastic diseases.

On the observation that the treatment with nitrogen mustard of transplanted lymphosarcoma in mice resulted in dissolution of the tumours, nitrogen mustard was used in the treatment of **leukaemia, Hodgkin's disease** and **lymphosarcoma.** Dramatic clinical improvement was observed in these conditions which lasted for weeks to months. The action of mustine is cytotoxic similar to that induced by X-rays.

It has proved effective in cases of **lymphadenoma** which were resistant to irradiation, **chronic myeloid leukaemia** and **polycythaemia vera,** although not so effective in acute leukaemia. Mustine is not curative but gives relief by reducing the total number of white blood cells with improvement of anaemia. The lymph nodes, liver and spleen diminish in size resulting in a feeling of well-being. Improvement however is rarely maintained and response to treatment appears to diminish on repetition.

These compounds are powerful irritants and therefore it is necessary to protect the skin or the mucous membrane. The margin of safety being small caution is necessary while using these drugs. Immediate and systemic effects are local pain, thrombophlebitis of injected veins ; nausea, vomiting, diarrhoea, malaise and vertigo may occur, but these are avoided by careful technique. More serious toxic manifestations are leucopenia, granulocytopenia, thrombocytopenia, and even severe anaemia. These are avoided by having the blood picture at frequent intervals and by adherence to safe dosage schedule.

To avoid nausea and vomiting the patient should not take any food for several hours before the injection and should be given a sedative and pyridoxine hydrochloride **2½ gr. (150 mg.)** prior to the injection of mustine

Dose and administration.—Usual dose is 0.1 to 0.2 mg. per kg. of body weight, dissolved in 10 to 30 mils of sterile normal saline solution, *intravenously* daily or on alternate days. Three to six injections constitute a course. Additional doses may be given but not oftener than every six to eight weeks and not more than 2 to 4

* *British Medical Journal,* May 27, 1945.

doses. Since the solution is quickly hydrolysed they should be freshly prepared and used within five minutes

FOLIC ACID ANTAGONISTS. (Not official)

The fact that several derivatives of liver extract inhibited the growth of experimental tumours in mice led to the trial of several folic acid derivatives in the treatment of malignant diseases in man. Of the various analogues employed **Aminopterin** was found to be effective though highly toxic.

Later, it was found that folic acid was essential for the growth of Rous sarcoma in chickens and this could be checked by the administration of folic acid antagonists. Aminopterin has therefore been used in the treatment of certain types of **neoplastic disease** not amenable to the usual therapeutic measures like irradiation, and other established procedures. It has been used in acute and subacute **leukaemia** where it causes remission of the disease. The mechanism of its action is not known and the toxic effects are not counteracted by folic acid.

Toxic reactions are stomatitis with ulceration of the mouth, purpura, leucopenia, diarrhoea, vomiting and alopecia.

The drug is in experimental stage and further experience is necessary before it can be adopted for treatment. It does not cure but gives relief of symptoms.

Dose.—The usual dose is 1 to 4 mg. (1/60 to 1/15 gr.) daily by the mouth for adults and 1 mg. daily for children, until there is haematological response or appearance of toxic symptoms.

PHENYLHYDRAZINE HYDROCHLORIDE. (Not official)

Till recently it was the only drug used in **polycythaemia** in doses of 50 mg. (3/4 gr.) three times a day *orally* for three or four days. It causes marked diminution of the red corpuscles. When the red cells come down to 4 or 5 millions per c.mm. the dose is reduced and 50 mg. being given every three or four days. It does not act on the bone-marrow but on the red blood corpuscle causing haemolysis and this effect continues for several weeks even after the use of the drug is stopped.

It is very toxic when given intravenously or subcutaneously. Common toxic symptoms are nausea, anorexia, vomiting, excessive haemolysis and severe secondary anaemia.

It has been replaced by radioactive phosphorus (*see* page 133).

2. Drugs used in agranulocytosis

Pentnucleotide, Pyridoxine Hydrochloride (see page 604), **Liver Extract** (see page 655), **Folic Acid**, (see page 658), **Penicillin** (see page 568).

INJECTIO NUCLEOTIDI, B. P. C. Syn.—Liquor Pentosi Nucleotidi.

A sterile solution containing about 8 p.c. of sodium pentose nucleotides. **Dose.**—150 to 300 ms. or 10 to 20 mils, by *intramuscular injection.*

Action and Uses

Nucleotides are **leucocyte stimulants** and help development of granulocytes specially when they are depressed. Injection of nucleotide is therefore used in the treatment of **agranulocytosis.** The solution is injected deep into the gluteal muscle in doses of 10 to 20 mils twice daily until the desired response is observed which takes about four to five days. In very bad cases it may be used intravenously diluted further with 90 mils of sterile water once daily. But it should not be given within two hours after a meal.

Class E : **Drugs or measures which increase the blood volume** **Saline, Gum Saline, Glucose Saline, Blood Transfusion**

WHOLE HUMAN BLOOD, B. P.

Whole Human Blood is blood which has been mixed with a suitable anticoagulant. The blood is withdrawn aseptically through a closed system of sterile tubing into sterile container in which the anti-coagulant solution has been placed before the container is sterilised. When the withdrawal is complete, the container is sealed and cooled to 4° to 6° and is opened only (*a*) for the purpose of withdrawing a sample of blood for direct matching with the recipient's serum, and (*b*) when the blood is administered.

Characters.—A deep-red fluid which on standing separates into a red sediment of blood corpuscles and a yellow supernatant layer free from visible products of haemolysis. The plasma may be clear, or their may be turbidity due to the presence of fat ; a layer containing emulsified fat may form on the surface.

Storage.—Whole Human Blood is kept in a sterile container, sealed so as to exclude micro-organisms, and kept at a temperature of 4° to 6° until required for use, except during any periods necessary for examination and transport at higher temperatures which should not exceed thirty minutes in all.

CONCENTRATED HUMAN RED BLOOD CORPUSCLES, B. P.

Prepared from one or more preparations of Whole Human Blood which are not more than seven days old and each of which has already been directly matched with the blood of the intended recipient.

A quantity of plasma and anticoagulant solution not less than 40 p.c. of the total volume is removed from the Whole Human Blood.

Characters.—A dark red fluid when prepared ; after standing the red corpuscles may form a sediment, leaving a supernatant layer of yellow plasma.

Storage.—Should be kept in a sterile container and sealed to exclude micro-organisms, stored at a temperature of 4° to 6°, and used not more than 24 hours after its preparation and not more than 8 days after the preparation of the Whole Human Blood from which it is made.

DRIED HUMAN PLASMA, B. P.

Dried Human Plasma is prepared by drying a pool of supernatant fluids which are separated by centrifuging or by standing from quantities of Whole Human Blood. The pool should be treated so as to destroy the causative agent of homologous serum jaundice ; if such a treatment is not applied, not more than ten separate donations are pooled. The pool is dried by freeze-drying or by any other method which will avoid denaturation of the proteins and will yield a product readily soluble in a quantity of water equal to the volume of liquid from which the substance was prepared.

Characters.—A light to deep cream-coloured powder. The substance dissolves completely in water equal in volume to that of the liquid from which the sample was prepared.

Storage.—It should be kept in a sterile container, sealed so as to exclude micro-organisms and stored so as to exclude moisture and at a uniform temperature below 20°, protected from direct sunlight.

DRIED HUMAN SERUM, B. P.

Dried Human Serum is prepared by drying Liquid Human Serum by freeze-drying or by any other method which will avoid denaturation of the proteins and will yield a product readily soluble in a

quantity of water equal to the volume of liquid human serum from which the substance was prepared.

Characters.—A light to deep cream-coloured powder or friable solid.

Storage.—It should be kept in a sterile container, sealed so as to exclude bacteria and stored so as to exclude moisture and at a uniform temperature below 20°, protected from direct sunlight.

LIQUID HUMAN SERUM, B. P.

Liquid Human Serum is the pool of fluids separated from blood withdrawn from human subjects and allowed to clot in the absence of any anti-coagulant. The pool is clarified by filtration under aseptic conditions and should be treated so as to destroy the causative agent of homologous serum jaundice ; if such a treatment is not applied not more than ten separate donations are pooled.

Characters.—A clear pale yellow liquid, free from red blood corpuscles or colouration by haemoglobin when examined with the naked eye.

Storage.—It should be kept in a sterile container, sealed so as to exclude micro-organisms and stored at a temperature of 10° to 20° protected from direct sunlight.

ACTION AND USES

Experience during the first World War (1914-18) showed that the most valuable single method of combating shock due to haemorrhage was by transfusion of whole or citrated human blood. This restores effective blood volume and increases oxygen carrying power. Usually one pint is sufficient but more may be necessary in severe cases. Whole human blood is also used to replace any of the normal constituents of blood which may be lacking partly or completely. The amount and the rate at which it is to be transferred depend upon the age of the patient, his general condition, the state of his circulatory system and the therapeutic indication for transfusion. The haemoglobin level of the average adult is raised by about 7 per cent. by 540 ml. of whole human blood.

Disadvantage of blood transfusion is that fatalities or severe reaction may occur if the blood of the donor and the recipient do not match with each other. Hence, preliminary to transfusion a compatibility test in the ABO and Rh system should be carried out between the serum of the recipient and the red corpuscles of the donor.

Whole human blood is collected, under sterile condition, from healthy human adults, not suffering from any transmittable disease, e.g. syphilis, malaria, jaundice, filaria, etc., or the haemoglobin value of whose blood in terms of the National Physical Laboratory Haldane Haemoglobinometer Colour Standard is less than 85 p.c.

The blood is collected into a citrate solution of acid reaction containing dextrose. In the following solution (recommended by the B. P. Addendum 1951) the red corpuscles of the blood may be preserved for 21 days :—

Sodium Acid Citrate 2.0 to 2.5 grm., Dextrose 3.0 grm., Water for Injection q.s. 120.0 mils.

This will prevent the coagulation of 420 mils of blood.

It is used up either immediately or preserved in "Blood Bank" for future use in emergent conditions. The whole blood even when preserved under ideal conditions does not keep well for an indefinite period and to be safe and effective should be used up within 3 weeks of its collection.

Concentrated human red blood corpuscles is whole human blood from which part of plasma and anticoagulant solution have been removed. It is prepared from citrated whole human blood, of not more than 7 days old and it should be used up within 24 hours of its preparation. It is used in the treatment of various forms of **anaemia** ; the haemoglobin level of the average adult is raised by about 15 per cent. by the concentrated human red blood corpuscles obtained from 1080 mil of whole human blood.

Human plasma and serum have been found more effective than whole blood in the treatment of

1. Shock unless accompanied by extreme blood loss.
2. Severe infections, as a means of supplying specific and non-specific antibodies.
3. Various conditions associated with hypoproteinaemia, such as nephrosis, chronic infections, repeated paracentesis, severe burns, ulcerative colitis, certain liver diseases.
4. Many blood dyscrasias, especially those characterised by haemolytic tendencies or fibrinogen deficiency.
5. Cerebral oedema accompanying various injuries and toxaemias.
6. Emergency treatment of acute haemorrhage until whole blood is available.

The most practical advantage of pooled human plasma or serum is that it may be used immediately at the time it is required without preliminary delay due to 'typing' and 'cross matching'. Plasma may also be quickly and simply administered under adverse conditions, if necessary, as no complicated transfusion apparatus or special assistance is required. It is a safe procedure, and large amounts of citrated plasma have been rapidly and repeatedly administered without causing untoward reactions. It has been shown that because of the high osmotic pressure exerted by the plasma proteins, plasma does not diffuse from the circulation due to capillary permeability as do crystalloid solutions ; consequently, it can be used to regulate effectively and in a physiological manner, the volume of the circulating blood. Another advantage is that serum or plasma does not cause further haemoconcentration, a condition which is usually already present in cases of shock and severe burns.

Liquid human plasma is the liquid portion of whole human blood and may be prepared by centrifuging citrated whole human blood. It is used in emergencies when

whole human blood is not available. Specially useful in patients suffering from shock, burns or crush injuries.

Liquid human serum is the liquid which separates from human blood which has clotted and may be prepared by allowing the blood to clot and then separating the serum under sterile condition. It has the same action and uses as liquid human plasma.

Dried human plasma and serum.—In an attempt to obviate inherent deficiencies of liquid plasma and serum which have to be stored and transported under refrigeration many methods of processing plasma or serum for purposes of preservation have been evolved. All processes have the common purpose of removing the moisture content of the plasma or serum proteins.

Of the many procedures which have been studied, one of the most effective, since it results in no detectable alteration in the serum or plasma solids, is the method of desiccating the serum or plasma from the frozen state under high vacuum. This unique method of rapid freezing and vacuum dehydration from the frozen state, which at times has been referred as the 'lyophile process' represents a revolutionary advance in the preservation of biological substances and has been successfully applied to a wide variety of therapeutic agents derived from living sources. By this means it has been possible to remove water from plasma or serum in such a way that its content of antibodies and complement suffers no detectable loss. Furthermore, the rate of subsequent deterioration is reduced to a small fraction of that which takes place in the liquid state. Dried plasma or serum retains its therapeutic value and remains stable for at least five years. The content of specific and non-specific antibodies, complement, and coagulating elements, together with three-fifths of the platelets, remain essentially the same as that of original fresh plasma. When reconstituted they have the same action and use as of the corresponding liquid preparations. These should be reconstituted by adding either water for injection, injection of sodium chloride or isotonic solution of dextrose and sodium chloride sufficient quantity to make up the original volume of liquid human plasma and should be used within three hours of reconstitution.

Disadvantage.—The transfusion of plasma or serum either liquid or reconstituted dried preparation carry the risk of transmitting homologous serum jaundice.

DEXTRAN. (Not official)

It is a polysaccharide having a molecular weight approximately that of serum albumin, viscosity between that of blood and plasma, and a specific gravity slightly above that of human plasma.

It is administered *intravenously* as a plasma substitute with the object of raising the colloid osmotic pressure of the plasma to a

normal level when deficient. It possesses the following advantages over non-protein colloids, *viz.* (*a*) it is free from acidic radicals and therefore not likely to form storage complexes; (*b*) it can be hydrolysed into glucose by acids and certain living organisms, therefore it may also be slowly metabolised in the human body. As a plasma substitute dextran does not fulfil the nutritive, buffering or immunological functions of plasma protein obtainable from whole blood, or human plasma or serum. It may, however, be of great value in emergency when biologic products may not be available for immediate use. Moreover, the potential danger of transmitting homologous serum jaundice with plasma or serum, and of malaria and perhaps other diseases with whole blood, is obviated.

It is of special value in cases of burns who require, on an average, 1 to 1½ litres of dextran for each 10 p.c. of the body area burned. But attempt should be made to limit the amount of dextran administered to 2,500 to 3,000 mils (proportionately less for children) and make up the deficit, if required, with plasma since excessive replacement of plasma protein with the polysaccharide dextran is undesirable.

When administered as a 6 per cent. solution in normal saline it produces immediate rise in the colloid osmotic pressure of the plasma, and this rise can be maintained till after some days the serum albumin returns to normal.

It is not free from danger when used intravenously. Reactions of anaphylactic or anaphylactoid nature have been recorded. If the molecules of the polysaccharide are too large, obstructive lesions of renal glomeruli may occur.

GROUP XXII

VOLATILE OILS

General Action of Volatile Oils

Micro-organisms.—The volatile oils are protoplasmic poisons and act as **antiseptics**, both when used externally and also when taken internally. Some are more powerful in this respect and these belong chiefly to the turpentine group and the empyreumatic oils are largely used as efficient antiseptics and disinfectants. This action depends upon their volatility and solubility in lipoids which enable them to enter the bacteria more easily. The only drawback is their insolubility in water.

Skin.—Applied to the unbroken skin they first stimulate then depress the local sensory nerves and produce irritation and itching followed by numbness. The irritation is accompanied by redness caused by dilatation of local blood vessels. Volatile oils are therefore **irritants, rubefacients** and **mild anaesthetics.** Some of them, *e.g.* turpentine, rosemary, cajuput, mustard, etc., are powerful irritants and counter-irritants. Others again affect in a specific manner the nerve endings conveying the sensation of cold. To this class belong the stearoptenes, particularly menthol.

Alimentary canal.—The same irritant effect is observed in the mouth and stomach. Taken freely diluted, as in the form of aromatic waters, they stimulate the

nerves of taste and produce a sensation of heat in the mouth and reflexly induce salivary and gastric secretions. In the stomach volatile oils are mild irritants and cause a sense of heat in the epigastrium and provoke appetite for food. This irritation reflexly stimulates the heart and the central nervous system. They are **stomachics, carminatives** and **mild antiseptics.** In concentrated form, or the more powerful ones, may give rise to gastro-enteritis with hiccough, vomiting and diarrhoea. The milder ones, *viz.*, anise, dill, cinnamon, peppermint, etc., are largely used as carminatives and flavouring agents. Lower down in the intestine they increase their movements in small doses, while in large doses decrease them. Clinically their use is followed by expulsion of gas and relief of colic, and they are largely used with purgatives to prevent griping. Some are **anthelmintics,** *e.g.* oil of chenopodium and thymol.

Nervous system.—In ordinary therapeutic doses the effect on the nervous system is purely reflex from the mouth and the stomach. The vessels of the skin dilate and there is a feeling of warmth and relief of chill. The vaso-motor, accelerator and the respiratory centres are stimulated causing a rise of blood pressure, acceleration of respiration and a feeling of general well-being. The nervous system is affected directly only in large doses. The cerebrum is first stimulated and then depressed, but this differs in different preparations. Turpentine causes less excitement but more drowsiness, whereas camphor stimulates the brain and produces excitement and convulsion.

Absorption and clearance.—Volatile oils are rapidly absorbed both from the stomach and intestine and are eliminated through the different secretions. They can be detected in the breath, urine and sweat, to which they impart their characteristic odour. They are excreted with the urine in combination with glycuronic acid and during excretion stimulate the renal cells and act as **diuretics.** Some, like sandal wood oil, cubebs, buchu, etc., are **genito-urinary antiseptics.** While excreted through the bronchial mucous membrane they stimulate the secretions of the bronchial glands and act as **expectorants** and **pulmonary antiseptics.** Some are extensively used as such but their value as antiseptic to the respiratory tract when used by the mouth is doubtful.

They circulate in the blood unchanged and cause **leucocytosis,** the polynuclear variety being mostly increased, due to their irritant action on the alimentary canal.

The volatile oils are classified as follows :—

Class A : Turpentine Group

1. Oils : **Oil of Turpentine, Terebene, Terpineol**
2. Resins and Oleoresins ; **Colophony, Myrrh, Storax, Balsam of Peru, Balsam of Tolu**
3. Empyreumatic Oils : **Tar and Coal Tar** (*see* antiseptics), **Oil of Cade**

Class B : Volatile Oils having Special Stimulating Effects on the Skin
Oil of Eucalyptus, Oil of Cajuput, Oil of Rosemary, Oil of Mustard, Capsicum, Oil of Turpentine

Class C : Genito-urinary Antiseptics and Diuretics
Oil of Sandal Wood (*see* page 420), **Buchu** (*see* page 421), **Juniper** (*see* page 415)

Class D : Nauseants
Asafetida, Valerian

Class E : Carminatives and Flavouring Agents
Cloves, Cardamoms, Caraway, Coriander, Anethi, Anise, Lemon, Fennel, Cinnamon, Nutmeg, Oil of Lavender, Oil of Peppermint, Ginger

Class F : Anthelmintics
Oil of Chenopodium (*see* page 395), **Thymol**

CLASS A : Turpentine Group

OLEUM TEREBINTHINAE

Oil of Turpentine. (Ol. Terebinth.)

Syn.—Rectified Oil of Turpentine.

Source.—An oil distilled from turpentine, the oleo-resin, obtained from various species of *Pinus*, and rectified.

Characters.—Limpid, colourless, liquid. Characteristic odour and a pungent, bitter taste. *Solubility.*—Soluble in 7 volumes of alcohol (90 p. c.), and in all proportions of alcohol (95 p. c.), of solvent ether, chloroform, and of acetic acid.

Composition.—Two isomeric bodies *d-* and *l*-pinene. Other constituents are *resin acids, camphene* and *fenchene. Dipentene* and polymeric *terpene* may also occur. Formic, acetic and camphoric acids and camphoric aldehyde.

B. P. Dose.—3 to 10 ms. or 0.2 to 0.6 mil.

OFFICIAL PREPARATION

1. **Linimentum Terebinthinae.—65 p. c.**

Terpini Hydras, B.P.C. *Syn.—Terpene Hydrate.*—Colourless, lustrous crystals or a white powder. Efflorescent ; action similar to turpentine, but less irritant, less disagreeable and less toxic. Diminishes cough and expectoration. Used in *bronchitis, phthisis* and *haemoptysis. Dose.*—3 to 10 gr. or 0.2 to 0.6 grm.

PHARMACOLOGY

Externally.—When rubbed into the skin, turpentine is a rubefacient, irritant and counter-irritant, and later on it depresses the sensory endings producing numbness. In large amounts it is a vesicant. It is also a local antiseptic and disinfectant, and it is absorbed by the unbroken skin.

Internally. **Gastro-intestinal tract.**—The same action is observed when taken internally, *i.e.* it dilates the gastric vessels, and increases both the peristaltic movements and the secretion of gastric juice. In the intestine it helps expulsion of flatus and is a strong carminative. In large doses it causes great vascular dilatation and purging, the stools containing large quantities of blood.

Respiration.—When inhaled it irritates the bronchial mucous membrane causing dilatation of the vessels, increase of the secretion, and stimulation of the muscular coats of the bronchi during excretion, and acts as an **expectorant.** If the secretion is purulent it is disinfected. Given by the mouth it is excreted by the bronchial mucous membrane and produces the same effects as when inhaled.

Nervous system.—In large doses it causes languor, hebetude, drowsiness and unsteadiness of gait. Toxic doses are followed by coma and paralysis of the sensory nerves with abolition of reflex action.

Kidneys.—Here its action is specially powerful. The renal vessels are dilated causing some diuresis. It appears in the urine in combination with glycuronic acid. Comparatively small doses may cause lumbar pain, scanty urine, albuminuria and haematuria, with all the symptoms of strangury. After a large dose there may even be complete suppression of urine. The urine has a smell of violet.

THERAPEUTICS

Externally.—Turpentine *stupes* (flannels wrung out of very hot water and sprinkled with turpentine) are largely used in tympanitic distension of the abdomen, and to produce irritant or **counter-irritant** effects in various forms of acute and chronic inflammation, such as pleurisy and bronchitis. The liniments are valuable applications to painful areas, as in neuralgia, myalgia, rheumatism and lumbago.

On account of its property of constricting the vessels, turpentine is used as a **haemostatic** to check the free oozing from many operations about the mouth, in which case its antiseptic properties are also of value.

Internally.—As an enema (60 to 120 ms. in 4 pints of water with soft soap), with or without castor oil, turpentine is used to relieve flatulent distension and to expel thread-worms. In doses of 120 to 240 ms., followed by a dose of castor oil, it is an anthelmintic for tape-worm, but it is rarely used now.

Given internally in small doses it is useful in chronic bronchitis and at one time was used as inhalation, but terebene and eucalyptus oil are more pleasant and less irritating.

Caution.—Turpentine must always be given cautiously on account of its liability to set up strangury, and *it should never be given at all to subjects of Bright's disease* as in cases of this kind it may cause fatal suppression of urine.

Terebenum, B.P.C. (Tereben.).—Terebene is obtained by steam distilling the product of the limited action of sulphuric acid on oil of turpentine.

Characters.—A colourless, or pale-yellow liquid, with a pleasant and characteristic odour; taste, aromatic, terebinthinate. Almost *insoluble* in water, miscible with dehydrated alcohol.

Composition.—A mixture of *dipentene* and other hydrocarbons.

Dose.—5 to 15 ms. or 0.3 to 1 mil.

NON-OFFICIAL PREPARATION

1. **Vapor Terebenae, B. P. C.**—Terebene 40 ms., Magnesii Carbonas Levis 30 grs., Water to 1 oz. A teaspoonful of this in a pint of water at 140°F. as an inhalation.

PHARMACOLOGY AND THERAPEUTICS

As an *expectorant*, terebene has been used in chronic bronchitis, winter cough and bronchiectasis, especially when complicated with

emphysema. It may be exhibited in various ways : (*a*) *Externally* ; either as an inhalation in the form of the vapour, or 15 to 30 drops may be sprinkled on the cotton-wool of an antiseptic respirator, or it may be used as a spray ; (*b*) *Internally*, as a mixture, either alone or combined with apomorphine and other expectorants ; or five drops may be taken a few times a day on a lump of sugar, or in capsules or thick syrup.

As an *antiseptic* and *sedative*, the vapour is useful in phthisis, and it is combined with equal parts of phenol and thymol, or phenol and spirit of chloroform. Use 10 drops of this mixture for medicating the antiseptic respirator. Terebene acts on the mucous membrane of the urinary and gastro-intestinal tract in much the same way as turpentine.

TERPINEOL.—$C_{10}H_{18}O$.—Terpineol is a mixture of isomers in which *dl-a*-terpineol largely predominates. Prepared by treating terpin hydrate with a dilute mineral acid and fractioning the crude product by distillation.

Characters.—A colourless, slightly viscous liquid, which may partially solidify ; odour, pleasant ; taste, characteristic, bitter and slightly pungent. Very *slightly soluble* in water ; soluble in alcohol (70 p.c.) and in solvent ether.

Enters into.—Liq. Chloroxylenolis.

USES.—It is an aromatic antiseptic used in the preparation of Liq. Chloroxylenolis and also to disguise the smell of iodoform.

COLOPHONIUM. (Coloph.). Colophony. **Syn.**—Rosin ; Resin.

Source.—The residue left after the distillation of the volatile oil from the oleo-resin obtained from various species of *Pinus*.

Characters.—Translucent, pale-yellow or brownish-yellow, angular, brittle, readily fusible, glassy masses ; odour and taste, terebinthinate. *Solubility.*—Freely in alcohol (90 p. c.), in solvent ether, benzene, carbon disulphide. Insoluble in water.

Composition.—It is an anhydride of three isomeric *abietic acids*, traces of a volatile oil, a *resene* and a bitter principle.

Enters into.—Collod. Flex.

ACTION AND USES.—Resin is an antiseptic and mild stimulant, and is therefore useful in indolent ulcers, wounds and sores. Basilicon ointment (colophony 26 p.c., yellow beeswax, lard and olive oil) is an excellent application for this purpose, but is apt to prove too stimulating if used for any length of time. Its chief use now is in pharmacy, to impart consistence and adhesiveness to plasters and ointments.

MYRRHA. (Myrrh.). Myrrh. **Syn. I. V.**—*Gandharasha, Gandhabol, Bol*, Beng.

Source.—An oleo-gum-resin obtained from the stem of *Commiphora Molmol*, and probably other species of *Commiphora*.

Characters.—Rounded or irregular tears, or masses of irregular tears varying in size ; reddish-brown or reddish yellow externally, dry, more or less covered with a fine powder ; brittle, fractured surface irregular, somewhat translucent ; of a rich brownish colour, oily, with whitish marks. Odour, aromatic. Taste, aromatic, bitter and acrid.

Composition.—(1) *Gum* 57 to 61 p.c. (2) A *resin, myrrhin* 25 to 40 p.c. (3) *Myrrhol*, a volatile oil 2.5 to 8 p.c. (4) A bitter principle.

Enters into.—Pil. Rhei Co.

OFFICIAL PREPARATION

1. **Tinctura Myrrhae.—20 p. c. B. P. Dose.—30 to 60 ms. or 2 to 4 mils.**

PHARMACOLOGY

Externally.—Like other oleo-resins, locally, myrrh is a mild antiseptic and stimulant to the ulcerated and mucous surfaces.

Internally. **Gastro-intestinal tract.**—The same action is noticed in the mouth, throat, stomach and bowels. It promotes appetite,

excites gastric secretion and peristalsis of the stomach and intestines and is therefore a stomachic and carminative.

Blood.—It increases the number of leucocytes, perhaps by stimulating lacteal activity. It stimulates phagocytosis.

Elimination.—It is excreted by the mucous membranes especially those of the respiratory and genito-urinary tracts, which it stimulates and disinfects ; hence it is an expectorant, emmenagogue and uterine stimulant.

THERAPEUTICS

Internally.—Myrrh makes a good **mouth-wash** (120 ms. of the tincture in 1 oz. of water) for aphthous and ulcerated tongue, relaxed throat and spongy gums. Its efficacy is increased if combined with borax. For receded and ulcerated gums, tinct. myrrhae and liquor iodi mitis make a superior preparation.

For its stomachic and carminative properties, myrrh is often used as an adjunct to purgatives. As a disinfecting expectorant, it is occasionally given in chronic bronchitis and bronchiectasis. For its emmenagogue property it is largely prescribed in **amenorrhoea,** in conjunction with aloes and iron. Some however doubt its emmenagogue action.

STYRAX PRAEPARATUS. (Styr. Praep.).

Source.—Prepared Storax is a balsam obtained from the wounded trunk of *Liquidambar orientalis*, purified by solution in alcohol, filtration, and evaporation of the solvent. Contains not less than **30 p.c. of the total balsamic acid.**

Characters.—A brown, viscous substance, transparent in thin layers ; odour and taste, agreeable and balsamic. Entirely *soluble* in alcohol (90 p.c.), partly soluble in solvent ether.

Composition.—Consists of a resin mixed with an oily liquid. The *resin* consists of *storesinol* combined with *cinnamic acid.* The oily liquid consists of *styrol. ethyl cinnamate* and styracin.

Enters into.—Tinct. Benzoini Composita.

ACTION AND USES.—Storax resembles benzoin and the balsams of Peru and tolu in its action. It is an ingredient of compound tincture of benzoin. An ointment (1 in 4) is a parasiticide in scabies. Mixed with an equal part or twice its bulk of olive oil, it kills *Sarcoptes hominis* and pediculi.

BALSAMUM PERUVIANUM. (Bals. Peruv.). Balsam of Peru.

Source.—A viscid balsam, exuded from the trunk of *Myroxylon Pereirae.*

Characters.—A viscid liquid, dark-brown in bulk, reddish-brown, and transparent in thin layers. Free from stickiness or stringiness. Odour, agreeable, balsamic and vanilla-like. Taste, burning, slightly bitter. *Insoluble* in water, soluble in chloroform, and in 1 volume of alcohol (90 p. c.).

Composition.—(1) A colourless, oily, aromatic liquid *cinnamein,* 53 to 66 p.c. and a dark resin 28 p.c. The liquid portion consists of benzyl cinnamate and benzoate of benzyl. (2) The resin consists of a resin alcohol with *cinnamic acid* and *benzoic acid.*

PHARMACOLOGY AND THERAPEUTICS

Externally.—Balsam of Peru is an antiseptic and parasiticide and may be applied to wound, indolent ulcers, bed-sores, etc. An ointment ($12\frac{1}{2}$ p.c. in simple ointment) cures sore nipples and cracked lips. An ointment (60 grs. to 1 oz. of soft paraffin) kills pediculi and the acarus scabiei and is more agreeable than sulphur.

Internally.—Like most volatile oils, it is a stimulant and carminative. During its elimination by the bronchial mucous membrane it stimulates and disinfects the bronchial secretion but it is seldom used internally.

BALSAMUM TOLUTANUM. (Bals. Tolu.). Balsam of Tolu.

Source.—Obtained by incisions from the trunk of *Myroxylon Balsamum.* Contains 35 to 50 p.c. of total balsamic acids.

Characters.—A soft, tenacious brownish-yellow or brown solid when imported; hardens on keeping; brittle in cold weather; transparent in thin films. Odour, aromatic, vanilla-like. Taste, aromatic. *Solubility.*—In alcohol (90 p.c.), in solvent ether, in chloroform and in solutions of fixed alkalies.

Composition.—(1) *Benzoic acid* 8 p.c. (2) *Cinnamic acid* 12 to 15 p.c. (3) A resin 80 p.c. yielding *tolu-resinotannol.* (4) 7.5 p.c. of an oily liquid consisting of *Benzyl cinnamate* and *Benzyl benzoate.* (5) 1.5 to 3.0 p. c. of a very fragrant volatile oil.

Enters into.—Tinct. Benzoin. Co.

OFFICIAL PREPARATIONS

1. **Syrupus Tolutanus.**—2.5 p.c. **B. P. Dose.—30 to 120 ms. or 2 to 8 mils.**
2. **Tinctura Tolutana.**—10 p. c. **B. P. Dose.—30 to 60 ms. or 2 to 4 mils.**

ACTION AND USES.—Its action resembles those of balsam of Peru. The syrup is used as a flavouring vehicle for cough mixture. The tincture is a feeble expectorant.

OLEUM CADINUM. (Ol. Cadin.). Oil of Cade. **Syn.**—Juniper Tar Oil.

Source.—An oily liquid, obtained by the destructive distillation of the woody portion of *Juniperus Oxycedrus.*

Characters.—A dark reddish-brown, or nearly black, viscid oily liquid. Odour, empyreumatic. Taste, aromatic, bitter, acrid. Very slightly *soluble* in water; partially in cold alcohol (90 p.c.); almost entirely in hot alcohol (90 p.c.); in 3 volumes of solvent ether and in chloroform.

Composition.—*Cadinene,* $C_{15}H_{24}$. a sesquiterpene.

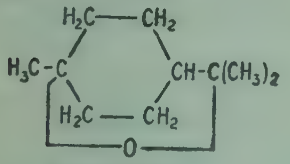
ACTION AND USES.—The oil of cade resembles tar in its action, but has a more pleasant odour. It is largely used in chronic eczema, psoriasis and other skin diseases like ring-worm and favus. It is applied in the form of an ointment (25 p.c.) combined with yellow beeswax and yellow soft paraffin, or simple cerate, or in a liquid form (oil of cade 1, soft soap 5, alcohol (90 p.c.) 4).

CLASS B: Volatile Oils having Special Stimulating Effect on the Skin

OLEUM EUCALYPTI

Oil of Eucalyptus. (Ol. Eucalyp.)

Source.—The oil distilled from the fresh leaves of various species of *Eucalyptus.* Contains not less than 70 p. c. of *Cineole,* $C_{10}H_{18}O$.



Eucalyptol

Characters.—Colourless or pale yellow liquid. Odour, aromatic, camphoraceous. Taste, pungent, leaving a sensation of coldness in the mouth. *Soluble* in 5 volumes of alcohol (70 p.c.).

Composition.—(1) *Eucalyptol* (cineole), a volatile oil. (2) A *terpene* called *phellandrene*; *butyric* and *valerianic aldehydes.*

B. P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

Eucalyptol. (Eucalyp.). Eucalyptol. **Syn.**—Cineole.

Source.—It is the anhydride of menthan-1 : 8-diol, and may be obtained from oil of eucalyptus.

Characters.—A colourless liquid; odour, characteristic, aromatic and camphoraceous; taste, pungent and cooling. *Soluble* in 2 volumes of alcohol (70 p.c.).

B. P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

NON-OFFICIAL PREPARATIONS

1. **Nebula Eucalyptolis Composita, B. P. C.**—Eucalyptol 80 mils, camphor and menthol, each 20 grms., thymol 1 grm., light liquid paraffin, *q.s.* 1000 mils.
2. **Vapor Mentholis et Eucalypti, B. P. C.**—Menthol 8 gr., oil of eucalyptus 60 ms., light magnesium carbonate 30 gr., water, *q.s.* 1 oz.

PHARMACOLOGY

Externally.—Oil of eucalyptus or eucalyptol is a powerful antiseptic and disinfectant. Rubbed into the skin it is

less irritant than other volatile oils, but if evaporation be prevented it causes rubefaction and vesication.

Internally. **Circulation.**—Like other volatile oils it stimulates the heart and raises the blood pressure reflexly through the stomach. In large doses the heart becomes weak and the blood pressure and temperature fall.

Clearance.—Like most of the volatile oils, eucalyptol is eliminated by the kidneys, the skin, and the respiratory and the genito-urinary mucous membranes, all of which it stimulates in the course of its passage. Like oil of turpentine it causes renal congestion and imparts to the urine an odour like that of violets.

THERAPEUTICS

Externally.—Because of its mild **antiseptic** and **anaesthetic** property, eucalyptol is extensively used as an inhalation in inflammatory conditions of the upper air passages as a spray or vapour. The oil mixed with mustard oil or olive oil may be rubbed into the skin in chronic rheumatism and myalgia. The vapour has been used as an inhalation in coryza, pulmonary gangrene, phthisis, chronic or foul bronchitis, etc.

Internally.—The most important use of eucalyptol or oil of eucalyptus is as an **expectorant** in chronic bronchitis, and catarrhal inflammation of the respiratory tract. Pastilles in combination with menthol are useful in colds with sorethroat. The oil may be used both orally or may be inhaled with steam with the addition of tincture of benzoin. To correct fetor of the expectoration or to cut short an attack of coryza, influenza, or catarrh, it may be used with benefit (5 to 10 drops of eucalyptol on sugar).

OLEUM CAJUPUTI. (Ol. Cajuput.). Oil of Cajuput. **Syn. I.V.** —*Kayaputir tel*, Beng. *Kayaputi ke tel*, Hind., Bom.

Source.—Distilled from the fresh leaves and twigs of *Melaleuca Leucadendron*, and other species of *Melaleuca*, and rectified by steam distillation. Contains 50.0 to 65.0 p. c. w/w of cineole, $C_{10}H_{18}O$.

Characters.—Colourless or yellow liquid ; odour, agreeable and camphoraceous ; taste, aromatic, bitter and camphoraceous. Colourless when rectified. *Solubility.*—In 2 volumes of alcohol (80 p.c.).

Composition.—(1) *Cineole* $C_{10}H_{18}O$, 50 to 60 p.c. (2) A crystalline *terpineol* ; *l-pinene* ; several *aldehydes*.

B. P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

OFFICIAL PREPARATION

1. **Spiritus Cajuputi.**—10 p.c. **B. P. Dose.—5 to 30 ms.** or **0.3 to 2 mils.**

PHARMACOLOGY AND THERAPEUTICS

Externally.—Oil of cajuput is used as a gentle counter-irritant on the chest in bronchitis, pneumonia, etc., and over painful and inflamed joints. It may be mixed with mustard oil or other stimulating and anodyne liniments.

Internally.—It is a powerful diffusible stimulant, carminative and antispasmodic. It is an excellent remedy for flatulent colic or intestinal spasm, sometimes relieving the pain by a single dose of

20 ms. of the alcoholic solution. For repeated administration an excellent combination is oil of cajuput 2 ms., thymol and menthol each 1/2 gr., chloroform pure 1 m., oleo-resin of capsicum 1 gr., in keratin coated capsules.

OLEUM ROSMARINI. (Ol. Rosmarin.). Oil of Rosemary.

Source.—The oil distilled from the flowering plant of *Rosmarinus officinalis.* Contains not less than 2 p. c. w/w of esters, calculated as *bornyl acetate,* and not less than 9 p. c. w/w free alcohols, calculated as *borneol,* $C_{10}H_{8}O$.

Characters.—Colourless or pale yellow ; odour of rosemary ; taste, warm, camphoraceous. *Solubility.*—1 in 1 of alcohol (90 p.c.).

Composition.—(1) *Borneol,* 8 to 16 p.c. (2) *Bornyl acetate* and other esters, about 2 to 5 p.c. Camphor, cineole, pinene and camphene.

Enters into.—Linimentum Saponis.

Action and Uses.—It is a stimulant and rubefacient to the skin, and is commonly used in the form of hair oil or hair wash to promote the growth of hair in **baldness.** Whitla recommends the following as a valuable application in baldness.* It is rarely used internally.

SINAPIS NIGRA, B.P.C.—Black Mustard consists of the dried ripe seeds of *Brassica Nigra.*

Composition.—Seeds contain glucoside *sinigrin* and an enzyme *myrosin.* In presence of water sinigrin is hydrolysed by the enzyme forming *allyl isothiocyanate,* C_3H_5NCS, also contains *allyl cyanide, carbon disulphide* and traces of *isomeric allyl thiocyanate.*

Oleum Sinapis Volatile, B. P. C.—Volatile Oil of Mustard.

Source.—The volatile oil distilled from *black* mustard seeds, deprived of most of their fixed oil and macerated in water for several hours.

Characters.—Colourless or pale yellow, intensely pungent and irritant with an acrid taste.

Non-official Preparation

1. **Linimentum Sinapis, B. P. C.**—Volatile oil of mustard 35 mils., camphor 55 grms., castor oil 125 mils., alcohol (90 p.c.) to 1000 mils.

Pharmacology

Externally.—Mustard is a powerful local **irritant, rubefacient and vesicant.** When it is first applied there is a sensation of warmth followed by severe burning pain, due to the irritant action of the mustard on the sensory nerves and increased local blood-supply. This irritation is quickly followed by paralysis, as a result of which there is loss of sensibility and a diminution both of the pain produced by the mustard and of any that may have existed previously. Mustard is also a **counter-irritant.** The excitation of the sensory nerves may reflexly stimulate the cardiac and respiratory centres.

Internally. **Gastro-intestinal tract.**—Taken in small doses as a *condiment,* mustard causes a sense of warmth in the stomach, stimulates the secretion of gastric juice and peristalsis and therefore sharpens the appetite. In large doses, it acts as a prompt and efficient *emetic* without causing the usual depression.

Therapeutics

Externally.—A linseed poultice, having a little mustard (1 in 16) dusted over it, is a very common and efficacious **irritant** and **counter-irritant** in rheumatism, pleurisy, pneumonia, and bronchitis.

A mustard plaster will **soothe pain** in gastralgia, colic, neuralgia, lumbago, etc. When put over the epigastrium it often relieves vomiting, and when applied to the calves of the legs, it is a reflex stimulant in cases of syncope, asphyxia and coma.

* Liq. epispast. 120 ms., Ol. rosmarin. 240 ms., Ol. amygdal. 1½ ozs., Sp. camph. 2 ozs., Glycer. acid. boric. 1 oz., Ol. rosae, 8 ms., Tinct. jaborand. 1 oz.

Severe headache, common colds and febrile conditions specially in children, are greatly relieved by hot pediluvium or foot-bath, whilst infantile convulsions may be checked by immersion of the whole of the patient's body in a mustard bath containing one tablespoonful of mustard to each gallon of warm water.

The volatile oil is a very powerful irritant and should be used diluted with alcohol or as the liniment; while the expressed oil is only mildly rubefacient and is used as a diluent for liniments.

Internally.—As an **emetic**, mustard is specially valuable in narcotic poisoning on account of its reflex stimulant effects. Give one to four teaspoonfuls in a tumbler of water.

Thiosinamina, B. P. C. **Syn.**—Allylthiocarbamide.—In white, glistening, prismatic crystals. Odourless, or have a faint garlic-like odour, taste, bitter. Soluble in 17 parts of water, in 2 parts of alcohol and in ether. *Dose.*—1/2 to 1½ gr. or 30 to 100 mg.

Action and Uses.—Thiosinamine has been used as injection to **soften scar tissue,** *e.g.* after burns, also in stricture of the oesophagus and urethra, hour-glass contraction of the stomach, Dupuytren's contraction, etc. It is used as a 10 p.c. solution in diluted glycerin in the region of the tissue to be absorbed. Prolonged use causes nausea, vomiting, pyrexia and sometimes purpura haemorrhagica.

CAPSICUM. (Capsic.). Capsicum.

Syn.—Small Chillies; Guinea Pepper; Pod Pepper; Capsici Fructus; *Dhani Lanka*, Beng. *Gach Marich*, Hind.

Source.—The dried ripe fruits of *Capsicum minimum.*

Characters.—Dull orange-red oblong, conical, obtuse two-celled fruits about 12 to 25 mm. long, up to 7 mm. wide; sometimes attached to a 5 toothed inferior calyx and a straight, slender pedicel. Pericarp somewhat shrivelled, glabrous, translucent, and leathery; containing 10 to 20 flat, reniform seeds, 3 to 4 mm. long. Odour, characteristic; taste, intensely pungent.

Composition.—(1) *Capsaicin* or *Capsacutin* (0.14 p.c.) a crystalline colourless pungent principle. (2) A liquid alkaloid. (3) An oleo-resin. (4) A fixed oil and red colouring matter.

Official Preparation

1. **Unguentum Capsici.** *Syn.—Chillie Paste.*—20 p. c. approximately.

Capsici Pulvis. (Capsic. Pulv.).—Powdered Capsicum is orange to brownish-red.

Official Preparation

1. **Tinctura Capsici.**—5 p.c. **B. P. Dose.**—5 to 15 ms. or 0.3 to 1 mil.

Pharmacology and Therapeutics

Externally.—Capsicum is a powerful irritant, rubefacient and therefore counter-irritant and may be used to promote the growth of hair. Emplastrum capsici (1 in 50 with resin plaster), or the ointment may be applied in rheumatism, lumbago or torticollis.

Internally. **Alimentary canal.**—In small doses it stimulates the secretion of saliva and gastric juice and increases peristaltic movements. It is therefore a sialagogue, stomachic and carminative. In large doses it is a gastro-intestinal irritant.

It is chiefly used as a condiment in India. It is an excellent remedy in atonic and flatulent dyspepsia and dipsomania.* In the last, it not only checks the craving but stimulates and tones the

* Tinct. capsic.	ms. 10
Sp. ammon. aromat.	ms. 30
Sod. brom.	grs. 10
Tinct. cinchon. co.	ms. 20
Aq. chlorof.	ad. oz. 1

gastric functions. The same prescription will generally be found to be an effective "pick me up."

Class C: Nauseants

ASAFOETIDA, I. P. L. (Asafoet.). Asafetida.

Syn. I.V.—*Hing*, Beng. *Hingra*, Hind., Bom.

Source.—An oleo-gum-resin obtained by incision from the living rhizome and root of *Ferula foetida*, *F. narthex*, or other species of *Ferula*.

Characters.—In rounded or flattened, or in masses, agglutinated; from 12 to 25 mm. in diameter, or dull yellow tears; darkening on keeping. Internally yellowish, translucent, or milky-white; opaque. Odour, strong, persistent, alliaceous. Taste, bitter, acrid, alliaceous. When triturated with water forms a white emulsion.

Composition.—(1) *Volatile oil*, 6 to 17 p. c. containing essential oil of garlic, allyl persulphide which gives it its peculiar odour. (2) A resin, *asaresinotannol*, 65 p. c. (3) *Gum*, 25 p. c..

Dose.—5 to 15 grs. or 0.3 to 1 grm.

Non-official Preparations

1. **Pilula Aloes et Asafoetidae, I. P. L.**—Aloes and asafetida, each 30 p. c. *Dose.*—4 to 8 grs. or 0.25 to 0.5 grm.
2. **Tinctura Asafoetidae, I. P. L.**—20 p. c. The resin is precipitated on addition of water. *Dose.*—30 to 60 ms. or 2 to 4 mils.

Pharmacology

Internally. **Gastro-intestinal canal.**—Like other volatile oils and resins asafetida is a stimulant, carminative and antispasmodic expelling flatus and relieving spasm; but its unpleasant nauseous taste is a drawback to its use.

Lungs.—It increases and disinfects bronchial secretion during its elimination. Hence it is a disinfectant expectorant.

Nervous system.—It reflexly stimulates the nervous system through the mouth and stomach.

Elimination.—By the bronchial secretion and urine.

Therapeutics

Externally.—A thick emulsion prepared by triturating asafetida with water is often applied with benefit to the abdomen of infants in tympanites.

Internally.—It is rarely used except as a sedative in hysteria and allied conditions and as a carminative in flatulence. In the latter condition it may be given as an enema (30 grs. rubbed up with water 4 ozs.). Cases of malingering may sometimes be cured by giving effervescing draughts containing a few minims of tinctures of asafetida and valerian, three or four times a day. The aloe and asafetida pill is used in mild forms of hysteria with menstrual disturbances and constipation.

VALERIANA. (Valerian.). Valerian. **Syn.**—Valerianae Rhizoma.

Source.—The rhizome and roots of *Valeriana officinalis*, collected in the autumn and dried.

Characters.—*Rhizome*: 2 to 4 cm. long, entire or longitudinally divided; yellowish-brown externally, whitish internally; fracture, short, and horny; cortex parenchymatous with starch grains; endodermal cells contain volatile oil. *Roots*: Numerous, slender, brittle, 2 to 10 cm. long. Odour, that of *iso*valeric acid; taste, sweetish, camphoraceous and slightly bitter.

Composition.—Its chief constituent is a volatile oil, 1 p. c., consisting of *bornyl isovalerate*, *formate*, *butyrate*, and *acetate*, united with *l-pinene*, *l-camphene*, and *l-limonene*. The oil has no odour when freshly distilled but on exposure to air develops the characteristic odour.

Valerianae Pulvis. (Valerian. Pulv.).—Powdered Valerian is light brown to greyish-brown.

Official Preparation

1. **Tinctura Valerianae Ammoniata.**—20 p. c. **B. P. Dose.—30 to 60 ms.** or **2 to 4 mils.**

Valeriana Indica, B. P. C. (Valerian. Indic.).—Indian Valerian consists of the dried rhizome and roots of *Valeriana Wallichii*. Contains not more than 2 p.c. of other organic matter.

Characters and Composition.—The same as Valerian.

Zinci Valerianas, B. P. C.—Zinc Valerianate.

Characters.—In white, pearly, tabular crystals with a characteristic disagreeable odour and metallic taste. *Soluble* in hot water and alcohol (1 in 60).

Dose.—1 to 3 grs. or 60 to 200 mg.

PHARMACOLOGY AND THERAPEUTICS

Small doses of valerian, like other volatile oils, produce a sensation of warmth in the epigastrium, a quickened pulse, and some mental excitement. It has recently been shown that valerian is a sedative to the sensory and psychic centres ; the motor centres remaining uninfluenced except by very large doses. It, therefore, controls nervous irritability, nervous insomnia and mental exhaustion.

The ammoniated tincture is useful as a carminative in flatulence ; and as a reflex stimulant in faintness and palpitation, but the essential oil (2 to 5 ms.) suspended in mucilage is better.

It is largely used in hypochondriasis, hysteria, nervous headache and other neurotic conditions in the form of the tincture with bromides, or as an extract (1 to 5 grs.) with camphor monobromata for its supposed action on the psychical functions and the circulation. Its effects are however purely mental produced by its unpleasant taste and odour. In fact most of these cases yield to suggestion and use of charms, etc.

CLASS D : Carminatives and Flavouring Agents

CARYOPHYLLUM

(Caryoph.). Clove.

Syn. I. V.—*Lobanga*, Beng. *Long*, Hind.

Syn.—Cloves ; Caryophyllus.

Source.—Clove consists of the dried flower-buds of *Eugenia Caryophyllus*.

Characters.—10 to 17.5 mm. long, bright reddish-brown, wrinkled, sub-cylindrical ; calyx, which tapers below is surrounded by four thick, rigid, patent teeth between which are four paler imbricated petals enclosing stamens and a single style. Odour, strong fragrant and spicy. Taste, very pungent, and aromatic.

Composition.—(1) *Volatile Oil* (*off.*) 15 to 20 p.c. (2) *Caryophyllin*, a crystalline body. (3) *Gallo-tannic acid.* (4) resin, etc.

Caryophylli Pulvis. (Caryoph. Pulv.).—Powdered Clove.

Enters into.—Pulv. Cret. Aromat. and Pulv. Cret. Aromat. c. Opio.

OFFICIAL PREPARATIONS

1. **Infusum Caryophylli Concentratum.—B. P. Dose.—30 to 60 ms. or 2 to 4 mils.**
2. **Infusum** Caryophylli.—2.5 p. c. Should be used within twelve hours of its preparation. **B. P. Dose.—1/2 to 1 oz. or 15 to 30 mils.**

Oleum Caryophylli. (Ol. Caryoph.).—Oil of Clove.

Source.—The oil distilled from Clove. Contains between 85 to 90 p. c. v/v of *eugenol*, $C_{10}H_{12}O_2$.

Characters.—Colourless or pale yellow liquid when recent, darkening with age or on exposure to air ; odour and taste, those of clove.

Composition.—(1) *Eugenol*, 85 p.c. chemically resembling phenol. (2) *Acetyl-eugenol*, about 10 p. c. (3) *Caryophyllene*, a sesquiterpene, furfural and methyl-amyl-ketone.

B. P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

Enters into.—Pil. Colocynth. et Hyoscy.

PHARMACOLOGY

Externally.—Oil of clove is rubefacient, counter-irritant and mild analgesic.

Internally. **Alimentary canal.**—In the mouth clove reflexly stimulates the secretion of saliva and mucus and sharpens the appetite by stimulating the nerves of taste and smell. Simultaneously, the gastric circulation is reflexly excited with increased flow of the gastric juice.

In the stomach it increases the secretion of the gastric juice and the peristaltic movements and acts as a stomachic and carminative. It is an **intestinal antispasmodic.**

Therapeutics

Externally.—The oil is sometimes used as an *anodyne* in superficial neuralgias. Very often it is employed for flavouring hair-oils and liniments. It is also very useful for *keeping off mosquitoes* for which purpose a little should be rubbed on the hands and feet immediately before retiring to rest.

Internally.—Clove is generally used in cookery to improve flavour, and with aromatic bitters, to stimulate appetite and digestion. The oil relieves toothache when put into the cavity of the decayed tooth. It is an excellent remedy for intestinal colic and flatulence. It may be combined with purgatives to prevent griping.

Prescribing hints.—The oil is best given on a lump of sugar or triturated with sugar as *eloeosacchara,* or suspended in mucilage.

CARDAMOMI FRUCTUS. (Cardam. Fruct.). **Syn.**—*Elachi,* Beng.—Cardamom Fruit consists of the dried, nearly ripe fruit of *Elettaria Cardamomum* var. *minuscula.* Odour and taste, of the seeds, strongly aromatic.

Enters into.—The seeds :—Ext. Colocynth. Co., Pulv. Cret. Aromat., Pulv. Cret. Aromat. c. Opio, Tinct. Gent. Co., Tinct. Rhei Co.

Official Preparation

1. **Tinctura Cardamomi Composita.—B. P. Dose.—30 to 60 ms. or 2 to 4 mils.**

Action and Uses.—Cardamom seeds are stimulant, stomachic and carminative and are therefore useful in flatulence and for correcting the griping property of purgatives. The tincture is a colouring and flavouring agent.

CARUM. Caraway. **Syn.**—Caraway Fructus ; Caraway Seed ; *Jira,* Hind.

Source.—The dried fruit of *Carum Carvi.*

Characters.—Mericarps separate ; each 7 mm. long, 2 mm. broad ; brown, with paler ridges ; slightly curved, tapering, glabrous. Odour, aromatic. Taste, aromatic, characteristic.

Composition.—(1) The *volatile oil* (*off.*).

Cari Pulvis. (Cari Pulv.).—Powdered Caraway is fawn to brown.

Enters into.—Tinct. Cardam. Co.

Oleum Cari. (Ol. Cari.). **Syn.**—Oleum Carui.—Oil of Caraway is the oil distilled from Caraway. Contains 53 to 63 p.c. w/w of Carvone, $C_{10}H_{14}O$.

Characters.—Colourless or pale yellow liquid, having the odour and taste of the fruit.

Composition.—(1) *Carvone,* an unsaturated ketone. (2) Terpene or *d*-limonene, also called *Carvene.* (3) *Cymene.*

B. P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.
Enters into.—Pil. Aloes.

Uses.—The same as those of anethi.

CORIANDRUM. (Coriand.). Coriander.
Syn.—Coriandri Fructus ; *Dhania,* Beng., Hind.
Source.—The dried ripe fruit of *Coriandrum sativum.*

Characters.—Nearly globular, 3 mm. in diameter, uniform, brownish-yellow, glabrous. Two mericarps closely united, and crowned by calyx teeth and stylopod. Odour, aromatic, especially when *bruised*. Taste, agreeable.
Composition.—The *Volatile Oil* (*off.*).

Coriandri Pulvis. (Coriand. Pulv.).—Powdered Coriander is fawn to brown.

Enters into.—Tinct. Rhei Co.

Oleum Coriandri. (Ol. Coriand.). Oil of Coriander.

Source and Characters.—A colourless or pale yellow oil obtained by distilling Coriander. *Solubility.*—1 in 3 of alcohol (70 p.c.).

Composition.—(1) *Coriandrol* the dextro-isomeride of linalol. (2) *d-pinene, l-pinene*, geraniol and borneol.

B. P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.
Enters into.—Elix. Casc. Sagr. and Ext. Senn. Liq.

The *action and uses* of coriander fruit resemble more or less those of dill and anise fruits. The oil is specially used to render medicines more palatable and to prevent griping. The fruit is used in Indian cookery, and its mericarps are chewed with prepared *pan* or sometimes alone to remove the after-taste of drugs.

ANETHUM. (Aneth.). Dill.
Syn.—Anethi Fructus ; *Soya*, Hind.
Source.—The dried ripe fruit *Anethum graveolens.*

Characters.—The fruit consists of two mericarps freed from pedicel. Each is broadly oval ; 4 mm. long, 2 to 3 mm. broad ; compressed dorsally ; brown, dorsal ridges inconspicuous, but lateral ones prolonged into *wings.* Each mericarp exhibits 6 vittae. Odour and taste, aromatic.
Composition.—The *Volatile Oil* (*off.*).

Anethi Pulvis. (Aneth. Pulv.).—Powdered Dill is pale brown.
Oleum Anethi. (Ol. Aneth.). Oil of Dill.
Source.—Obtained by distilling Dill. Contains 43 to 63 p.c. w/w of *carvone* $C_{10}H_{14}O$.

Characters.—A colourless, or pale yellow, liquid, darkening with age ; odour, that of the fruit ; taste, at first sweet and aromatic, subsequently pungent. *Soluble* in equal volume of alcohol (90 p. c.), and in 10 volumes of alcohol (80 p. c.).
Composition.—(1) A *Terpene* (*d-limonene*), *Carvone.*

B. P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

Official Preparation

1. **Aqua Anethi Concentrata.**—Oil of dill 2 p. c. **B. P. Dose.—5 to 15 ms. or 0.3 to 1 mil.**

Action and Uses.—Dill and oil of dill are aromatics, stimulants, antiseptics, and carminatives and are used to relieve flatulence and intestinal colic. The oil corrects the griping of purgatives. Dill water is chiefly used to remove flatulence in children.

OLEUM ANISI. (Ol. Anis.). Oil of Anise.

Source.—Obtained by distilling dried ripe fruits of *Pimpinella Anisum*, or from the dried fruits of the star anise, *Illicium verum.*

Characters.—Colourless, or pale yellow, liquid ; odour, that of the fruit ; taste, mildly aromatic.
Composition.—(1) *Anethole* 80 to 90 p. c. *Anisic aldehyde.* (3) *Methyl chavicol.*

B. P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.
Enters into.—Elix. Casc. Sagr. and Tinct. Opii Camph.

Action and Uses.—The action and uses of anise are almost identical with those of dill, except that it has a slight expectorant property and is often prescribed as a vehicle for cough mixtures.

LIMONIS CORTEX SICCATUS. (Limon. Cort. Sicc.).—Dried Lemon Peel is the dried outer part of the pericarp of the ripe, or nearly ripe, fruit of *Citrus Limon.*

Characters.—Strips or pieces ; outer surface, yellow and somewhat rough, with only a small amount of the white spongy part of the pericarp on the inner surface. Odour, aromatic ; taste, aromatic, bitter.
Enters into.—Inf. Gent. Co. Conc.

LIMONIS CORTEX RECENS. (Limon. Cort. Rec.).—Fresh Lemon Peel is the outer part of the fresh pericarp of the ripe or nearly ripe, fruit of *Citrus Limon.*

OFFICIAL PREPARATIONS

1. **Syrupus Limonis.**—Peel 6 p. c. **B. P. Dose.—30 to 120 ms.** or 2 to 8 mils.
2. **Tinctura Limonis.**—Peel 25 p. c. **B. P. Dose.—30 to 60 ms.** or 2 to 4 mils.

Oleum Limonis. (Ol. Limon.).—Oil of Lemon is the oil expressed from fresh lemon peel. Contains not less than 4.0 p. c. w/w of aldehydes, calculated as citral, $C_{10}H_{16}O$.

Characters.—A pale yellow or greenish-yellow, liquid ; odour, that of lemons ; taste, warm and slightly bitter.
Enters into.—Sp. Ammon. Aromat. and Tinct. Valerian. Ammon.

ACTION AND USES.—The action of lemon peel is similar to that of orange peel. The oil is a stimulant and carminative and can be used to expel intestinal flatus. In practice both of them are used for flavouring purpose. Lemon juice is antiscorbutic and contains vitamin C.

FOENICULUM. (Foenic.). Fennel.
Syn. I. V.—*Bari Sanf, Saurif,* Hind.
Source.—Fennel consists of the ripe fruits of *Foeniculum vulgare* from cultivated plants.

Characters.—Mericarps up to 10 mm. long, 4 mm. broad ; small, oblong, curved, glabrous ; greenish-brown or pale-yellowish brown. Odour, aromatic. Taste, aromatic, sweet. The fruit is readily separated into 2 mericarps each of which has 5 prominent primary ridges, and exhibits in transverse section 6 large vittae.
Composition.—(1) A *Volatile oil,* 3 to 4 p. c. which contains *anethole* and *fenchone.*

Foeniculi Pulvis. (Foenic. Pulv.).—Powdered Fennel is greenish-yellow to yellowish-brown.

Enters into.—Pulv. Glycyrrhizae Co.

USES.—The same as those of anise or of dill.

CINNAMOMUM. (Cinnam.). **Syn.**—Cinnamon Bark. *Dalchini,* Beng.
Cinnamon is the dried inner bark of the shoots of coppiced trees of *Cinnamomum zeylanicum,* and is known in commerce as Ceylon cinnamon.

Characters.—Single or double, closely packed compound quills, up to a metre or more in length, and about 1 cm. in diameter. Outer surface, dull yellowish-brown, marked with pale, wavy longitudinal lines, and with occasional small scars or holes ; inner surface, darker in colour, striated with a longitudinally elongated reticulation. Brittle, fracture splintary. Odour, fragrant ; taste, warm, sweet and aromatic.
Enters into.—Tinct. Catechu.

Cinnamomi Pulvis. (Cinnam. Pulv.).—Powdered Cinnamon is dull yellowish-brown.

Enters into.—Pulv. Cret. Aromat., Pulv. Cret. Aromat. c. Opio, Tinct. Cardam. Co.

Oleum Cinnamomi. (Ol. Cinnam.). Oil of Cinnamon.
Source.—The oil distilled from Cinnamon. Contains 50.0 to 65.0 p.c. w/w cinnamic aldehyde, C_9H_8O.

Characters.—A yellow liquid when freshly distilled, gradually becoming reddish-brown with age ; odour and taste, those of cinnamon.
Composition.—(1) *Cinnamic aldehyde,* 50 to 65 p. c. (2) *Cinnamic acid.* (3) *Eugenol.*

B. P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

OFFICIAL PREPARATION

1. **Aqua Cinnamomi Concentrata.**—Oil of cinnamon 2 p.c. **B. P. Dose.**—7 to 15 ms. or 0.3 to 1 mil.

The action and uses of cinnamon oil resemble those of cloves and the oil of cloves but the bark has besides a mild astringent property. The oil is used in combination with other drugs as an intestinal antiseptic in typhoid fever. It is perhaps useful in preventing tympanitic distension.

MYRISTICA. (Myrist.). Nutmeg.

Syn. I.V.—*Jaiphal*, Beng., Hind.

Source.—The dried kernel of the seeds of *Myristica fragrans.*

Characters.—Broadly oval or rounded, about 20 to 30 mm. long. Externally, greyish-brown, with reticulated furrows. Internally, greyish-red marbled with brownish-red veins. Odour, strong, aromatic. Taste, aromatic, warm, bitter.

Composition.—(1) A *fixed oil* consisting of glyceryl oleate, glyceryl butyrate and glyceryl myristate, 25 to 30 p.c. (2) *Amylodextrin.* (3) *Volatile oil* (5 to 15 p.c.).

Myristicae Pulvis. (Myrist. Pulv.).—Powdered Nutmeg is reddish-brown.

Enters into.—Pulv. Cret. Aromat. and Pulv. Cret. Aromat. c. Opio.

Oleum Myristicae. (Ol. Myrist.). Oil of Nutmeg.

Source and Characters.—A pale yellow oil, distilled from nutmeg, having the odour and taste of nutmeg. *Solubility.*—1 in 3 of alcohol (90 p.c.).

Composition.—(1) *Myristicin*, terpene. (2) A terpene, *d-camphene.*

B. P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.
Enters into.—Sp. Ammon. Aromat., Tinct. Valerian. Ammon.

Pharmacology and Therapeutics

Externally.—The volatile and the fixed oils are used for perfuming pomades and lotions for the hair, and diluted with olive oil or soap liniment as an embrocation in chronic rheumatism. Nutmeg made into a paste is sometimes used in headaches and neuralgia.

Internally.—For its agreeable aroma it is used in cooking. Both the kernel and the volatile oil are gastric stimulants, increasing the flow of gastric juice, and are carminatives expelling intestinal flatus ; hence they can be used in dyspepsia, cramps and flatulence. The volatile oil relieves toothache, and the kernel is chewed to remove fetor of breath. In large doses it acts as a powerful narcotic, causing giddiness, vertigo and coma, symptoms resembling those that follow poisonous doses of camphor ; with some it may produce motor stimulation.

OLEUM LAVANDULAE. (Ol. Lavand.). Oil of Lavender.

Source.—The oil distilled from the fresh flowering tops of *Lavandula officinalis.* Contains (English oil) 7.0 to 12.0 p.c. w/w, or (foreign oil) not less than 35.0 p.c. w/w, of esters, calculated as linalyl acetate, $C_{12}H_{20}O_2$.

Characters.—A colourless, pale yellow or yellowish-green liquid ; odour, that of the flowers ; taste, pungent and slightly bitter.

Composition.—(1) *Linalol*, an alcohol, and its acetic ester, *linalyl acetate*, are the principal constituents. (2) Pinene, $C_{10}H_{16}$, present in some samples but is not a constant constituent. (3) Limonene, geraniol and a sesquiterpene.

Enters into.—Lint. Camph. Ammon.

Non-official Preparation

1. **Tinctura Lavandulae Co., B.P.C.**—Oils of lavender and rose, cinnamon bark, nutmeg, red sanders wood and alcohol (90 p.c.). *Dose.*—30 to 60 ms. or 2 to 4 mils.

Pharmacology and Therapeutics

Externally.—Oil of levender is used to perfume liniments, and the tincture to colour lotions. It is an ingredient of smelling salts and lavender water.

Internally.—Like other aromatic oils, it can be used as a carminative and antispasmodic in flatulence, colic, hypochondriasis,

hysteria and neurasthenic affections. The tincture is used for colouring and flavouring purposes.

OLEUM MENTHAE PIPERITAE. (Ol. Menth. Pip.). Oil of Peppermint.

Source.—The oil distilled from fresh flowering tops, *Mentha piperita* and rectified. Contains 4.5 to 9 p.c. w/w *menthyl acetate*, and 45.0 p.c. w/w free *menthol*.

Characters.—Colourless, pale yellow or greenish-yellow when fresh, becoming darker by age. Odour of the herb. Taste, aromatic, followed by a sensation of coldness. *Solubility.*—1 in 4 of alcohol (70 p. c.).

B. P. Dose.—1 to 3 ms. or 0.06 to 0.2 mil.
Enters into.—Cataplasma Kaolini, Pil. Rhei Co., Tab. Sod. Bicarb. Co.

Official Preparations

1. **Aqua Menthae Piperitae Concentrata.**—Oil of peppermint 2 p.c. **B. P. Dose.—5 to 15 ms., or 0.3 to 1 mil.**
2. **Emulsio Menthae Piperitae.**—10 p.c. **B. P. Dose.—5 to 30 ms. or 0.3 to 2 mils.**
3. **Spiritus Menthae Piperitae.**—10 p. c. **B. P. Dose.—5 to 30 ms. or 0.3 to 2 mils.**

Pharmacology and Therapeutics

Externally.—Owing to the presence of menthol, the sensation of coldness and numbness after a feeling of warmth is more marked. Hence, it is a mild analgesic and is therefore used to allay the pain of superficial neuralgias and muscular rheumatism. It is also a powerful antiseptic. It relieves toothache due to a carious tooth. The smell of the oil keeps off mosquitoes.

Internally.—For its powerful antispasmodic and carminative properties, it is often used as lozenges to relieve flatulent colic and spasmodic pains of the stomach. It corrects the griping effect of purgatives and covers the nauseous taste of drugs.

ZINGIBER. (Zingib.). Ginger.

Source.—Ginger is the rhizome of *Zingiber officinale*, scraped to remove the dark outer skin, and dried in the sun. Known in commerce as unbleached Jamaica ginger.

Characters.—Flattish, irregularly branched pieces, about 7 to 15 cm. long, 1.5 to 6.5 cm. wide ; 1 to 1.5 cm. thick ; each branch crowned by a depressed scar. Externally pale buff, striated, fibrous. Fracture, short, rather fibrous. Odour, well known, agreeable, and aromatic. Taste, strong, pungent.

Composition.—(1) An aromatic volatile oil, 1 to 3 p. c. (2) *Gingerol*, a yellowish oily body to which pungency is due. (3) Resin and starch.

Zingiberis Pulvis. (Zingib. Pulv.).—Powdered Ginger is light yellow.

B. P. Dose.—5 to 15 grs. or 0.3 to 1 grm.
Enters into.—Pulv. Rhei Co.

Official Preparations

1. **Tinctura Zingiberis Fortis.** *Syn.—Essence of Ginger.*—**B. P. Dose.—5 to 10 ms. or 0.3 to 0.6 mil.**
2. **Tinctura Zingiberis Mitis.**—1 in 5 of strong tincture. **B. P. Dose.—30 to 60 ms. or 2 to 4 mils.**
3. **Syrupus Zingiberis.—B. P. Dose.—30 to 120 ms. or 2 to 8 mils.**

Action and Uses—Ginger is a powerful aromatic stimulant, acting like capsicum and cardamoms. Chewed, it is a valuable sialagogue ; and used as snuff, it is a powerful errhine, but it is chiefly used as a stomachic, carminative and flavouring agent. Commercial gingerin, which is an oleo-resin, is a useful addition to purgative pills to prevent griping. The dose is 1/4 to 1 gr.

GROUP XXIII

SOLID VOLATILE OILS (Stearoptenes)

Camphor, Menthol, Thymol

CAMPHORA

(Camph.). Camphor. $C_{10}H_{16}O$

Syn. I. V.—*Karpur*, Beng. *Kafur*, *Kapur*, Hind.

Source.—Camphor is a white crystalline substance obtained from *Cinnamomum Camphora*, and purified by sublimation (natural camphor); or it may be obtained synthetically.

Characters.—Colourless, transparent, crystals, or crystalline masses of tough consistence; also in rectangular tablets or pulverulent masses, "Flowers of Camphor." Readily pulverisable in the presence of little alcohol (90 p.c.), solvent ether and chloroform. Odour penetrating. Taste, bitter, pungent, followed by a sensation of cold. Burns and volatilises. *Solubility.*—1 in 700 of water, 1 in 1 of alcohol (90 p. c.), in 0.25 of chloroform; very soluble in solvent ether. It forms a liquid when triturated with chloral hydrate, menthol, phenol, thymol.

B. P. Dose.—2 to 5 grs. or 0.12 to 0.3 grm.

Enters into.—Inj. Bism. Salicyl., Lin. Aconit., Lin. Bellad., Lin. Sap., Lin. Terebinth., Ung. Hydrarg. Co.

Official Preparations

1. **Aqua Camphorae.**—0.1 p. c. **B. P. Dose.—1/2 to 1 oz. or 15 to 30 mils.**
2. **Linimentum Camphorae.** *Syn.—Camphorated Oil.*—20 p. c. w/w of camphor.
3. **Linimentum Camphorae Ammoniatum.** *Syn.—Lin. Camphor. Co.*—12.5 p.c. w/v of camphor.
4. **Spiritus Camphorae.** *Syn.—Tinct. Camphorae.*—10 p.c. **B. P. Dose.—5 to 30 ms. or 0.3 to 2 mils.**
5. **Tinctura Opii Camphorata.** *Syn.—Tinct. Camphor Co.; Paregoric.*—0.05 p. c. of morphine, or 1/30 gr. morphine in 60 ms. **B. P. Dose.—30 to 60 ms. or 2 to 4 mils.**

Non-official Preparations

1. **Linimentum Chloroformi, B. P. C.**—Camphor liniment and chloroform equal quantity.
2. **Linctus Opii Camphoratus Co., B. P. C.**—Tr. opii camphor. 15 ms., syr. virg. prune 12 ms., oxymel of squill 12 ms., chloroform 3/8 m., sol. bordeaux 5/8 m., tr. seneg., q.s. 60 ms. *Dose.*—30 to 120 ms. or 2 to 8 mils.
3. **Naristillae Chlorbutolis, B. P. C.**—Chlorbutol 4 gr., camphor 6 gr., ol. cinnam. 4 ms., arachis oil 120 ms., liquid paraffin, q.s. 1 oz.*
4. **Camphorae Monobromata.**—In colourless prisms, insoluble in water. A hypnotic and nervous sedative in *hysteria, chorea, delirium tremens* and *petit mal*, also used in *spermatorrhoea*. *Dose.*—2 to 8 grs. or 0.12 to 0.5 grm.

Pharmacology

Externally.—Camphor acts like volatile oils. It is moderately **antiseptic**, though weaker than many volatile oils, *e.g.* the coal-tar series; or the phenol group of drugs. It stimulates the local vessels and causes redness and heat, thus acting as a rubefacient and counter-irritant. It first stimulates, then depresses the sensory nerves producing a sensation of coolness, and acts as a local anodyne.

Internally. **Alimentary tract.**—Camphor has a peculiar bitter taste and produces a sensation of coldness soon followed by that of warmth in the mouth. It stimulates the local circulation and the secretion of saliva and mucus in the mouth. In the stomach it (1) causes a feeling of warmth, (2) dilates the blood-vessels, (3) increases the flow of gastric juice, and (4) stimulates the peristaltic movements and causes relaxation of the sphincters. It is

*Naristillae or Nasal Drops.

therefore a gastric stimulant and **carminative**, but in large doses it irritates the stomach and causes nausea and vomiting. Injected into pigeons in sub-convulsive doses it causes vomiting within a few minutes by directly stimulating the vomiting centre in the medulla. It is a feeble antiseptic to the intestine and relieves spasm. It is slowly absorbed and after absorption transformed into camphoglycuronic acid.

Fig. 38.—Cat under urethane Records of blood pressure and respiration (Figures below indicate rates of respiration). At the first arrow 0.1 mil acetone and at the second arrow 15 mg. camphor dissolved in 0.1 mil acetone were injected.

Note.—After acetone, only slight fall in blood pressure and slight increase in respiratory rate. After camphor a well marked fall in blood pressure which soon recovers, the respiration stops for a very short duration followed immediately by increase in rate and amplitude.

Heart and circulation.—The knowledge of the action of camphor on the heart and circulation is uncertain although it is used as a circulatory stimulant. A moderate dose of camphor taken in solution reflexly stimulates the heart like other volatile oils. While some observers reported rise of pressure by stimulating the vaso-motor centre, others a persistent fall after a brief rise due to peripheral vaso-dilatation. No rise of pressure is observed in either anaesthetised, decerebrate or spinal animals. In fact it causes a fall of pressure by its action on the inhibitory centre in the medulla, since this is not marked in spinal animals. In some experiments it has been observed to stimulate the heart, while others did not observe any change. It probably stimulates the cardiac muscle. The coronary vessels are dilated but it is not certain whether this occurs in therapeutic doses (Cushny). It has been suggested that although camphor has no action on the normal heart, it improves the heart which is depressed or irregular. It dilates the vessels of the skin and gives a sensation of warmth like alcohol. It is possible that by dilating the vessels of the skin and the coronary arteries it effects a re-distribution of the blood much in the same way as strychnine. Being an irritant when given as an injection, it provokes reflex medullary stimulation (Gunn). But a more plausible explanation is that by stim-

ulating respiration it increases the oxygen supply to the heart and indirectly acts as a cardiac stimulant.

Respiration.—Camphor slightly stimulates the bronchial secretion by increasing the vascularity of the bronchial mucous membrane and acts as a feeble **expectorant.** Respiration is stimulated reflexly from the stomach like other volatile oils, and also directly by acting on the centre in the medulla. This effect is more marked when the respiration is previously depressed by some narcotics, like phenobarbitone or morphine. It increases both the rate and amplitude.* (*See* Fig. 38).

Nervous system.—Camphor stimulates the cerebrum and in moderate doses produces excitement, giddiness, confusion of ideas, and inco-ordination of movement, and in toxic doses convulsion by acting on the medulla since this is observed in decerebrate animals and not in spinal animals even in large doses. Convulsions are clonic and not of spinal origin like strychnine. This increased excitability and irritability is marked even in deeply narcotised animals. Loss of consciousness and stupor may appear later. With some it acts as an **exhilarant,** causing agreeable hallucinations with a desire to laugh or dance, and with others no excitement is observed, the effect being one of depression with drowsiness and stupor. It first stimulates and then depresses the reflex movements and acts as an antispasmodic. It **stimulates** the mid-brain and the **medullary centres,** chiefly the respiratory, vagal and vomiting centres and acts as an **analeptic** (*see* page 217).

Skin.—Some dilatation of the skin vessels follows the use of camphor by the mouth, due possibly from gastric irritation. It is excreted with the sweat, which it increases.

Temperature.—It has very little effect on temperature in health, but is a mild **antipyretic** in fever, due chiefly to loss of heat from dilatation of the skin vessels.

Clearance.—Camphor is partially oxidised in the tissue forming camphorol which combines with glycuronic acid and is excreted by the kidneys. This synthesis is carried out by the liver.

Acute toxic action.—Poisoning by camphor is rare. Epigastric pain, nausea, sometimes vomiting, giddiness, dimness of sight, delirium verging on mania, epileptiform convulsions, cyanosis, paralysis, cold clammy perspiration, strangury or arrest of urinary secretion, coma and death.

Treatment.—Emetics, pump, brisk saline cathartics, cold and hot douches, counter-irritation, sometimes stimulants, and strychnine hypodermically if necessary. Barbiturates for convulsion. Since alcohol and oils favour absorption, these should be avoided.

* B. N. Ghosh *et al.* Jour. Ind. Med. Assoc. June, 1942.

THERAPEUTICS

Externally.—Camphor is a favourite ingredient of many liniments for lessening the pain of fibrositis, myalgia and chronic rheumatism. The ammoniated camphor liniment combined with the turpentine liniment is an effective counter-irritant in bronchitis, pleuritis and broncho-pneumonia. Mixed with zinc ointment (30 grs. to 1 oz.) it allays the itching of eczema genitalis. Chloral-camphor and menthol-camphor are valuable local anodynes in superficial neuralgias.

Internally. **Alimentary canal.**—Mixed with chalk it is used as tooth-powder (1 in 8). Chloral-camphor relieves toothache when put into a carious tooth. Camphor water is a domestic carminative for flatulence and colic of children. Spirit of camphor may be given in flatulence and colic of adults. Spirit of camphor 15 ms. with chloroform is useful in sea-sickness, due possibly to its carminative action. Very few drugs can excel camphor in summer diarrhoea and in early cholera. It should be given in these cases from the commencement of the illness in 5 to 10 ms. doses of the spirit every 10 or 15 minutes till the symptoms abate ; and then hourly. It is useless in the later stages.

Respiratory tract.—The inhalation of camphor or its use in the form of snuff relieves coryza and that form of chronic catarrh which is characterised by paroxysmal sneezing. At the same time 5 drops of the spirit should be given by the mouth every 15 minutes. It is especially useful in chronic bronchitis when given either in the form of paregoric or with other expectorants.

Circulation.—Camphor is absorbed very slowly from the alimentary tract, it should therefore be used hypodermically as a circulatory stimulant. It is used to stimulate the heart in the later stages of infectious fevers, pneumonia, septicaemia, etc. Dissolved in oil or ether (1 to 2 grs. in 1 mil) it is valuable in threatened failure of the heart and respiration. But many doubt its efficacy.

Nervous system.—In many spasmodic affections, such as nervous palpitation, chorea, hysteria, etc., it has been given with doubtful results.

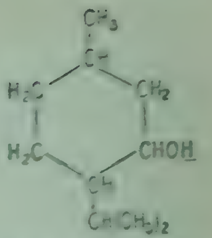
N.B.—Camphor is used to test the detoxicating power of the liver. After administration of 0.5 grm. (8 grs.) of camphor if no glycuronic acid is found in the urine within 24 hours, the liver function is impaired.

MENTHOL

Menthol. $C_{10}H_{20}O$

Source.—Menthol is laevo-menthol, natural or synthetic, or racemic menthol.

Characters.—Colourless acicular or prismatic crystals. Odour, penetrating resembling that of peppermint; taste, warm and aromatic, followed by a sensation of cold. Solubility.—Very slightly in water, readily in alcohol (90 per cent), in solvent ether, and in chloroform; freely soluble in light liquid paraffin, and in essential oils.



NON-OFFICIAL PREPARATIONS

1. **Nastillae Chlorbutolis cum Menthole B. P. C.**—Menthol ¼ gr. to Nastillae Chlorbutolis 1 oz.

2. **Menthyl Valerianate.** *Syn.*—*Validol.*—A solution containing 30 p.c. of menthol valerianate. A colourless liquid with an agreeable smell and no burning taste. **Nervous sedative; used in** *sea sickness, hysteria* and *neurasthenia. Dose.*—10 to 15 m. either in wine or on a lump of sugar.

4. **Nebula Mentholis et Thymolis Co., B. P. C.**—Menthol and camphor, each 10, thymol 2, pinene 25, paraffin liquid, q.s. 1000.

PHARMACOLOGY AND THERAPEUTICS

Locally applied menthol causes first stimulation, soon followed by a feeling of coldness, numbness and partial analgesia of the part, and thereby relieves the pain of neuralgias and other superficial pains. This is done by either drawing over the skin solid menthol, or by painting it with a liquefied preparation, such as menthol cum camphor, menthol cum chloral, or by applying a plaster. Any painting near the eyes causes a free flow of tears from the vapour. As a plaster, or when used with camphor, or with A.B.C. liniment, it is useful in rheumatic and pleurodynic pains, lumbago and sciatica. Mentholeate (menthol and oleic acid equal quantity), alcoholic solution (1 in 8), or menthol ointment (5 to 30 grs. in 1 oz. of vaseline or simple ointment) relieves pruritus. The ointment is specially useful in pruritus pudendi et ani.

Menthol, when rubbed up with either thymol, phenol, chloral hydrate, or camphor forms an oily liquid, which is largely used for toothache. It should be put into the cavity of the carious tooth and covered with a pledget of absorbent cotton. As a snuff (menthol 5 grs. in 1 oz. of starch, talc or oxychloride of bismuth) it is efficacious in influenza, hay fever, catarrh and ozaena.

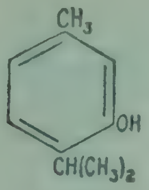
Menthol is also a powerful **antiseptic** and **antiparasitic,** and its alcoholic solution (1 in 20) is useful in ringworm **of the scalp.**

Pastilles containing menthol and oil of eucalyptus often relieves nasal and bronchial catarrh, and the nebula is used as a spray in naso-pharyngeal catarrh. It is rarely used internally, except as a corrigens of griping purgative pills, and in ½ to 1 gr. doses with extract of belladonna in flatulence and intestinal colic.

THYMOL

Thymol. $C_{10}H_{14}O$

Source.—A crystalline phenol obtained from the volatile oils of *Thymus vulgaris*, of *Monarda punctata*, and of *Trachyspermum Ammi*, or **prepared synthetically.**



$C_{10}H_{14}O$

Characters.—Colourless crystals ; odour, pungent, aromatic and thyme-like ; taste, pungent and aromatic. Sinks in cold water. *Soluble* in 1000 parts of water, in 1 part of alcohol (90 p.c.) in 1.5 parts of solvent ether, and in 0.6 part of chloroform.

B. P. Dose.—1/2 to 2 grs. or 30 to 120 mg. ; 15 to 30 grs. or 1 to 2 grms. *as anthelmintic.*

Enters into.—Cataplasma Kaolini.

NON-OFFICIAL PREPARATIONS

1. **Volckmann's Thymol Solution.**—Thymol 0.1, alcohol 2, glycerin 2, dissolve and add water to 100. As a *spray* and *antiseptic lotion.*
2. **Liquor Thymolis Co., B. P. C.**—Boric acid 26.4, benzoic acid 1.14, menthol 0.33, thymol 0.57, eucalyptol 1.25, ol. peppermint, methyl salicyl., ol. thyme, each 0.3, alcohol (90 p.c.) 250, water, q.s. 1000.
3. **Naristillae Mentholis et Thymolis, B. P. C.**—Menthol 2 gr., thymol 1 gr., eucalyptol 1 m., liquid paraffin q.s. 1 oz.
4. **Solvellae Thymolis Co., B. P. C.**—Sod. bicarb. 5 gr., borax 5 gr., phenol 1/2 gr., thymol 1/20 gr., amaranth 1/100 gr.*

PHARMACOLOGY AND THERAPEUTICS

Externally.—Thymol is a very powerful antiseptic about 25 times more powerful than phenol and less toxic to the tissues, but its insolubility is its drawback. A solution of the strength of 1 in 1000 stops all putrefactive or fermentative action in any fluid to which it is added. Volckmann's solution is used in *antiseptic surgery* and the ointment (20 gr. in soft paraffin 1 oz.) is very useful in parasitic skin diseases, especially tinea of the scalp or beard. The pastilles, spray and inhalation are useful in laryngitis and pharyngitis.

Internally.—In large doses, thymol gives rise to very unpleasant symptoms, excitement, vertigo, etc., and the urine may become green. In still larger doses the medullary and spinal centres are paralysed, collapse sets in, and there is a marked fall of blood pressure and temperature before death. It is for the greater part broken down in the body and about 25 p.c. is excreted unchanged in the urine.

A lotion (1 in 2000 to 1 in 1000) is used as a mild antiseptic mouth-wash. It inhibits the growth of *Laptothrix buccalis*, and is a slowly acting obtudent for hypersensitive dentine. Thymol was formerly used as an anthelmintic for hookworm, but because of its toxicity it has been replaced by other safer drugs (see page 394). It is usually given in doses of 15 to 30 grs. repeated 3 or 4 times at intervals of an hour ; 60 grs. should be the maximum dose for a healthy adult, but usually 45 grs. would suffice. It should be given on an empty stomach followed by a purgative. Such large doses however may cause abortion in women, therefore when treating pregnant women the dose should not be more than 30 grs. given in three doses of

*Solvellae or solution-tablets. These are tablets intended to be dissolved in water for external or local use only.

10 grs. each. For the weak, anaemic, and those with bad heart the dose should be less.

Prescribing hints.—As an anthelmintic thymol *should not be administered in solution*, as it causes a most unpleasant burning sensation of the mouth and throat and is extremely irritating to the stomach. It should be given in pill or cachet. The patient must keep to his bed and lie down for several hours after the last dose; he must also be warned not to partake of alcohol, or any other solvent of thymol as long as the drug is in his stomach. It is not a suitable drug for the old or for children. It should be followed by a saline purge, and castor oil should not be used.

GROUP XXIV

ANTISEPTICS, DISINFECTANTS AND PARASITICIDES

(Anti-infectives)

Antiseptics or *bacteriostatics* are substances which prevent or retard the growth of micro-organisms as long as they remain in contact with them but do not destroy them.

Disinfectants, bactericides or *germicides* destroy pathogenic microbes, *i.e.* those which cause communicable diseases; *deodorants* destroy offensive or disagreeable odours.

Antiparasitics or *parasiticides* kill parasites infesting the surfaces of the body.

In dilute solutions most disinfectants act as antiseptics, yet many antiseptics while retarding the growth of micro-organisms do not act as efficient disinfectants, either because they become inert when they come in contact with organic matter, or are too poisonous to be used for a prolonged period. A large number of disinfectants, however, act upon most forms of living matter and are *general protoplasmic poisons* and have no specific action on microbes in preference to tissues. Therefore ordinary disinfectants while destroying microbes also cause damage to the tissues in which they are lodged. Since efficient disinfection also entails destruction of the surrounding cells, it is impossible to use a drug to disinfect the tissues of the body as a whole in sufficient concentration to destroy only the microbes without injuring the tissues. Quite recently however great progress has been made in this direction. A dye compound under the name of *Prontosil* has been introduced and found to be potent against certain bacteria and has been successfully used in the treatment of certain infections in human subjects. Several derivatives have since been introduced which possess unique bactericidal properties and have revolutionised the outlook and treatment of bacterial diseases. Further advance in this direction is the introduction of penicillin and other antibiotics. These are classed as *systemic anti-infectives.* (*see* page 548).

An ideal disinfectant will exert a maximum action on

the micro-organisms, *i.e. parasitotropic,* and a minimum action on the body tissues, should be soluble in water or will form a uniform emulsion in all proportions, rapid in action and non-corrosive to metals. Browning and his associates have shown that certain basic substances like flavine and acriflavine act more powerfully in the presence of serum, stimulate granulating processes, are not irritating to the tissues, and do not interfere with phagocytosis. These derivatives therefore are the nearest approach to ideal antiseptics.

The exact manner in which the disinfectants act is not fully understood. The degree of ionisation of a solution may possibly have an important bearing on its disinfecting efficiency. Briefly disinfectants act (*a*) by oxidising the protoplasm of the bacteria, *e. g.* the halogen compounds, bleaching powder and potassium permanganate liberate nascent oxygen ; (*b*) by coagulating the protoplasm of the bacteria, *e. g.* the phenols and their derivatives ; (*c*) by ionic coagulation, *e.g.* the metallic salts ; (*d*) by abstraction of water (desiccation) ; and (*e*) by emulsoid action and adsorption. Admitting the value of the disinfectants, there are certain limitations. For instance, the presence of electrolytes may lower their value ; oxidising agents give up oxygen so rapidly that they soon become inert and lastly the metallic disinfectants do not penetrate readily. The temperature has also some significance. For instance, the germicidal value of phenol increases 7 to 8 times with every 10°C. rise of the temperature. Warm solutions are therefore more useful and should be used.

The choice of a germicide depends on the nature of the substance to be disinfected and upon the resistance of the organisms. Thus, perchloride of mercury 1 in 1000 solution, or phenol 2.5 per cent. solution will not kill the spores of tetanus.

The factors which influence the action of disinfectants are many, *viz.*—(*a*) the nature of the invading organism and the number present ; (*b*) the nature and strength of the antiseptic used and the extent to which its action is affected by the presence of organic matter ; (*c*) the time taken by the disinfectant to act efficiently ; (*d*) the nature of the solvent used ; and (*e*) the temperature.

The following are the requirements of an efficient disinfectant :—

1. It must be a powerful germicide and rapid in action and should possess great power of penetration.
2. It should have a definite efficiency for particular organisms under given conditions, and should be permanently homogeneous.
3. The chemical properties should be such as will render it fit for ordinary use and not become inert by faecal or any polluting material, *i.e.* it should be stable in the presence of organic matter.
4. It should not have any injurious effects on human tissues and materials submitted for disinfection.
5. It should be soluble in water or form a uniform emulsion in all proportions.
6. It should be fairly cheap, and should not act on metal, bleach pigment or spoil fabrics, and be neither toxic nor caustic.
7. It should have a high solvent power for grease.

Standardization of Disinfectants.—In order that the different disinfectants may be used with some amount of precision it is essential to have some idea of the relative potency of these substances. Therefore a standard method of testing the various disinfectants under precisely similar conditions is of considerable importance. This is done by comparing with phenol, a method devised by Rideal and Walker. The minimal concentration of phenol which will kill a

twenty-four hours' culture of *Bact. typhosus* in a certain length of time is first determined, and then the concentration of some unknown disinfectant which will produce the same effect under the same conditions is determined. The concentration of the phenol thus obtained, divided by the concentration of the unknown disinfectant gives a figure which is known as the *Rideal-Walker or Carbolic Acid Coefficient* of the disinfectant tested. A low carbolic coefficient expressed as a number less than unity usually means that the substance possesses slight disinfecting value.

Class A : General Antiseptics and Disinfectants
Class B : Systemic Anti-infectives (*see* Sulphonamides and Penicillin, page 548).
Class C : Intestinal Antiseptics (*see* page 361)
Class D : Urinary Antiseptics (*see* page 416)
Class E : Pulmonary Antiseptics (*see* page 342)
Class F : Parasiticides

I. General Antiseptics and Disinfectants

The drugs of this group are used for a wide variety of purposes. Apart from their use in surgical practice for disinfecting infected wounds, the skin, or to sterilise surgeon's hands and instruments, they have a greater field of usefulness in preventive medicine. To be of value the disinfectant must be used in solution or suspension in water and the strength should be such as will not cause much irritation of the tissues or the skin. For surface disinfection the oxidising disinfectants are sufficient to destroy the microbe, but for wounds it is necessary that the drug should penetrate into the tissues to reach the organisms and this implies some destruction of the nervous structures and of the tissues in which they are imbedded causing certain amount of pain and irritation, consequently all efficient disinfectants are local irritants. Moreover, some of them may be absorbed when applied to a large surface and exhibit poisonous symptoms. Owing to these effects it has been found that a wound heals less quickly when strong antiseptics are used and therefore their use is now confined only to those cases that are already infected, or there is possibility of infection, and no antiseptics are used in clean cases. In fact these heal more rapidly without the use of any antiseptics.

The general antiseptics are :—

1. Oxidising Agents
   Hydrogen Peroxide, Potassium Permanganate, Potassium Chlorate (*see* page 81)
2. **Halogens and their Compounds**
   Chlorinated Lime, Chloramine, Dakin's Solution, Eusol, Iodine, Iodoform
3. Heavy Metals
   Mercury (*see* page [illegible]), Silver Salts (*see* page 12[illegible]), Copper Sulphate (*see* page 12[illegible]), Ferrous Sulphate (*see* page 66[illegible]), Zinc Salts (*see* page 124)
4. Coal-tar Compounds
   Phenol, Cresol, Chlorocresol, Chloroxylenol, Resorcinol, Trinitrophenol, **Coal-tar, Tar, Betanaphthol, Salol, Coal-tar Dyes**
5. Quaternary Ammonium Compounds
   Cetrimide (Cetavlon)
6. Miscellaneous Compounds
   Formaldehyde, Boric Acid, Borax, Sodium Metabisulphite.

1. Oxidising Agents

LIQUOR HYDROGENII PEROXIDI

(Liq. Hydrog. Perox.)

Syn.—Liquor Hydrogenii Dioxidi.

Source.—Solution of Hydrogen Peroxide may be obtained by the interaction of water, barium peroxide, and dilute sulphuric acid, at a temperature below 10°C. Contains 5 to 7 p.c. w/v of H_2O_2, corresponding to about 20 times its volume of available oxygen.

Characters.—A colourless, odourless liquid with a slightly acid taste. Rapidly decomposes in contact with certain metals, oxidisable organic matter, also if allowed to become alkaline.

Pharmacology and Therapeutics

Hydrogen peroxide is a powerful antiseptic and disinfectant by virtue of its oxygen which it gives off when brought into contact with many substances including all forms of living matter, pus, blood, bacteria, etc. It is not an irritant and being non-poisonous is largely used. Its effects, however, last only for a short time, for as soon as the oxygen is liberated it becomes inert. When injected directly into the blood it forms gas embolism causing death of the animal.

It is largely used in general and dental surgery, also many cosmetics owe their efficacy to its presence. As a cleansing agent a solution (1 in 8) may be used with benefit in sores, foul suppurating wounds, chancre and fetid discharges from the ear.

It is much employed as a gargle, or mouth wash, as in diphtheria, or pyorrhoea alveolaris, or for deeply furred tongue, and as a surgical cleanser in pus conditions. In pus cavities the oxygen is freed with great rapidity, and the pus corpuscles are said to be disintegrated.

POTASSII PERMANGANAS

(Pot. Permang.). $KMnO_4$.

Source.—Potassium Permanganate is obtained by the action of carbon dioxide on an aqueous solution of potassium manganate. Contains not less than 99 p.c. of potassium permanganate.

Characters.—Dark purple, slender, prismatic crystals, having a metallic lusture ; odourless ; taste, sweet, astringent. *Solubility.*—1 in 20 of water.

Incompatibles.—Iodides, organic substances and any reducing agent.

B. P. Dose.—1 to 3 grs. or 60 to 200 mg.

Non-official Preparations

1. **Liquor Potassii Permanganatis.**—1 p.c. Has a disagreeable taste. **Condy's fluid** is only of half the strength, and contains soda salt. *Dose.*—120 to 240 ms. or 8 to 15 mils.

2. **Calcium Permanganate.**—Crimson, deliquescent crystals ; soluble in water. Useful in *enteritis* and *cholera*. *Dose.*—1/2 to 1½ grs. or 30 to 100 mg.

Pharmacology

Externally.—Potassium permangnate in its solid form is an irritant and even caustic, and in solution a stimulant. It is a valuable **oxidising agent,** giving off oxygen when moist and in the presence of organic matter, thus destroying decomposing ferments and septic germs. It is an **antiseptic, deodorant** and **disinfectant.** The only drawback is that it yields up oxygen too quickly rendering it inert after a short time ; consequently its germicidal powers are limited.

Internally.—It is an unstable compound, being decomposed into manganese dioxide in the stomach, in which form it is probably absorbed. Manganese has no direct haematinic property but is intimately related to iron metabolism specially in conjunction with copper, *i.e.* helps absorption of iron. When injected into the blood, or subcutaneously, it is excreted by the intestine and kidneys.

THERAPEUTICS

Externally.—Potassium permanganate is used for its disinfectant and deodorant properties for disinfecting stools and foul discharges, washing bed pans, and articles and hands after contact with infectious diseases. Being odourless and non-irritant, it is best suited for use at the bedside. Fabrics are stained by it, but the stain is easily removed by sulphurous acid ; but they must be immediately washed, otherwise they would be damaged by the sulphuric acid formed. Because of its oxidising property rather than its disinfectant action, it is used (2 grs. in 10 oz. of distilled water) as a cleansing agent for foul and suppurating ulcers, abscesses, and as a vaginal or uterine douche. It was formerly largely used for irrigating the urethra in gonorrhoea. A saturated solution (1 in 20) is an excellent application in bites by poisonous snakes and rabid dogs, if it can be immediately applied. Application of permanganate crystals after free incision is the treatment of snake-bite. It is largely used for sterilising water of wells, etc.

Internally.—Potassium permanganate makes a very effective gargle (2 grs. to 10 ozs. or the liquor diluted to 1 in 50) in foul and ulcerative diseases of the gums, mouth and throat. On account of its powerful oxidising property it is used to render certain poisons harmless, and therefore has been recommended in phosphorus, hydrocyanic acid, opium, morphine and other alkaloidal poisoning. A 0.2 per cent. aqueous solution is generally used for the purpose of washing out the stomach.

It is said to assist utilisation of iron in the formation of haemoglobin in the treatment of microcytic anaemia.

It is usually administered in the form of pill made with some inert powder and soft paraffin and should not be mixed with any oxidisable substance.

A drink of calcium permanganate 4 grs. to one pint of boiled water, *ad libitum*, together with pills of potassium permanganate 2 grs. each (salol coated) every half an hour until the stools become greenish has been used in cholera. It is rarely used now.

2. Halogens and their Compounds

CALX CHLORINATA

Chlorinated Lime. (Calx Chlorinat.)

Syn.—Bleaching Powder. Chloride of Lime.

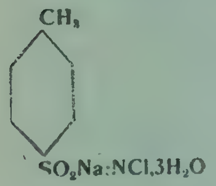
Source.—Obtained by the action of chlorine upon calcium hydroxide. Contains not less than 30 p.c. w/w of available chlorine.

Characters.—A dull, white powder ; odour, characteristic. Becomes moist and gradually decomposes on exposure to air. *Solubility.*—Partly in water and alcohol (90 p.c.).

Liquor Sodae Chlorinatae Chirurgicalis. (Liq. Sod. Chlorinat. Chir.). **Syn.**—Dakin's Solution.

Surgical Solution of Chlorinated Soda is prepared by combining chlorinated lime, sodium carbonate, boric acid and distilled water in proper proportions indicated in the B. P. Contains not less than 0.50 p.c. w/v, and not more than 0.55 p.c. w/v, of available chlorine.

Chloramina. (Chloram.). Chloramine. **Syn.**—Chloramine-T.



Source.—It is sodium *p*-toluenesulphonchloroamide.

Characters.—White crystals, or crystalline, powder ; odour, that of chlorine ; taste, unpleasant, bitter. Effloresces and slowly decomposes on exposure to air, losing chlorine and assuming a yellow colour. *Soluble* in about 7 parts of water, in 2 parts of boiling water, and in 12 parts of alcohol (90 p. c.).

NON-OFFICIAL PREPARATIONS

1. **Liquor Calcis Chlorinatae cum Acido Borico, B. P. C.** *Syn.—Eusol.*—Chlorinated lime and boric acid powder, each 55 gr., water to 10 oz.

2. **Dichloramina.** *Syn.—Dichloramine-T.*—Contains 28 to 30 p. c. of active chlorine. Gradually decomposes and loses chlorine on exposure to air. Pale yellow crystals, or yellow crystalline powder with odour of chlorine.

3. **Anti-gas Ointment No. 1.** *Syn.—Bleach Ointment.*—Equal parts by weight of bleaching powder and white soft paraffin. Used as antidote to cases exposed to liquid mustard gas. To be rubbed in immediately and washed off after one minute.

4. **Anti-gas Ointment No. 2.**—Contains chloramine-T in a vanishing cream basis. Used as a phophylactic and antidote to the effects of mustard gas on the skin.

PHARMACOLOGY

Externally.—Chlorine has a great affinity for hydrogen and consequently decomposes chemical and organic compounds which contain it, such as ammonia, sulphuretted hydrogen, and many organic matters. It is a powerful poison to all living matter and bacteria, but since it is a violent irritant it is not used in surgical practice except in the form of different compounds which give off chlorine more slowly. Applied to the skin for a long time, as in the case of workmen in a manufactory of bleaching powder, it causes itching, redness and inflammation, leading even to vesication or sloughing. Inhaled in a concentrated form it is a powerful irritant to the respiratory passages and may cause death from spasm of the glottis or inflammation of the air-passages.

All these compounds are highly efficient **disinfectants** and **deodorants** and part with their available chlorine in a few minutes in the presence of excess of proteins, consequently their disinfectant action is very rapid. The chlo-

rine combines with all forms of proteins specially the amine groups forming chloramine which is a powerful antiseptic and kills any micro-organism with which it comes into contact ; but if there is an excess of protein the available chlorine is rapidly exhausted and it ceases to have any antiseptic or disinfectant property. The chloramines so formed being soluble, the hypochlorites dissolve organic matter and dead tissues. The relative action of the different preparations depends on their content of available chlorine. Chloramine solutions are more stable, neutral, less irritating and more efficacious as they do not give up the whole of the available chlorine as rapidly as the others.

Internally.—It exerts the same local influence on the parts with which it comes in contact, until decomposed into chlorides in the stomach, when it loses its virtues as an uncombined element.

THERAPEUTICS

Externally.—Because of its efficiency and cheapness, chlorinated lime is largely used for disinfection of stool, urine, sputum and similar matters. For disinfection of stool sufficient bleaching powder should be intimately mixed with the excreta and allowed to stand for one to two hours. One pound of chlorinated lime in a bucket-full of water makes an all-round efficient disinfectant for washing floors, privies, and other places with offensive effluvia, not only for its germicidal but for its deodorizing effect. It may also be used for disinfecting infected articles like plates, cups, etc.

Chlorinated lime and liquid chlorine are largely used for sterilising drinking water and swimming baths. One drachm of bleaching powder is dissolved in a pint of water and a tea-spoonful of this will purify two gallons without imparting any taste to the water. For swimming baths the concentration necessary to keep the water pure is 0.2 part per million.

Chlorinated lime is used as a neutralising agent for chemicals of the mustard gas type. It reacts quickly with the gas and decomposes it. The Anti-gas Ointment may be applied to the skin within three minutes of exposure and wiped off after one minute.

A mixture of equal parts of chlorinated lime and boric acid (Eupad) is a useful application to septic areas. The gas evolved acts more powerfully than eusol, specially when moistened between layers of gauze or lint and covered with wool and bandaged.

Eusol, Chloramine-T, and Dakin's solution are largely used as non-irritating and inexpensive antiseptics for wounds and ulcers, and for washing cavities with foul discharges and as a nasal or vaginal injection, etc. Since the

chlorine or hypochlorite is rapidly used up by contact with the proteins of the inflamed surface, continuous saturation of wounds is necessary, and this will abolish sepsis, dissolve dead tissue and promote healing. Dakin's solution is one of the most suitable and stable forms of chlorine for this purpose. Hypochlorite solution (1 p.c.) sprayed into a room prevents **droplet infection** ; while Dichloramine-T in oily solution (2 p.c.) is used as a nasal spray for **carriers** of meningococcus.

Internally.—The different solutions are used as gargles (chloramine 0.5 p.c.) in malignant sore throat, diphtheria, mercurial salivation, and sloughing stomatitis.

IODUM

Iodine. (Iod.)

Source.—Obtained from naturally occurring iodides and iodates.

Characters.—Heavy, bluish-black, brittle, rhombic prisms or plates with a metallic lustre ; odour, characteristic. Volatilises at ordinary temperatures. *Slightly soluble* in water, more in alcohol (90 p.c.), soluble in chloroform, in solvent ether, glycerin and carbon disulphide. Freely soluble in aqueous solutions of iodides.

Incompatibles.—Alkalies and alkaline carbonates, oil of turpentine, most volatile oils, tannin and vegetable astringents.

Official Preparations

1. **Liquor Iodi Fortis.** *Syn.—Tinct. Iodi Fort. ; Lin. Iodine.*—Contains 10 p.c. w/v of iodine, and 6 p.c. w/v of potassium iodide.

2. **Liquor Iodi Mitis.** *Syn.—Tinct. Iodi Mitis ; Tinct. iodi.*—Contains 2.5 p.c. of iodine, and 2.5 p. c. of potassium iodide, or about 4/5 gr. of iodine (1 1/5 gr. total iodine) in 30 ms. **B. P. Dose.—5 to 30 ms. or 0.3 to 2 mils.**

3. **Liquor Iodi Aquosus.** *Syn.—Lugol's Solution ; Liquor Iodi Co.*—Contains 5 p.c. w/v of iodine, and 10 p.c. w/v of potassium iodide ; or 4/5 gr. of iodine, and about 2 grs. of total iodine in 15 ms. **B. P. Dose.—5 to 15 ms. or 0.3 to 1 mil.**

Non-official Preparations

1. **Pigmentum Iodi Co., B. P. C.** *Syn.—Mandl's Paint.*—Iodine 12.5, pot. iodid. and water, each 25.0, ol. peppermint 4.2, alcohol (90 p.c.) 37.5, glycerin q.s. 1000.0.

2. **Entodon.**—*Hexamethyl-diamino-isoproponal-di-iodide.*—A water-soluble iodine preparation. Used either *subcutaneously* or *intravenously. Dose.*—1/2 to 1 ampoule or 1 to 2 mils.

Pharmacology

Externally.—The action of iodine is identical with that of chlorine, *i.e.* it unites with amine group of proteins, with this difference that iodamines are insoluble and being less volatile, iodine is a slower bactericide than chlorine, though more lasting. Its inhalation produces irritation of the respiratory passages, cough, sneezing, frontal and thoracic pain and dyspnoea. It is a powerful **antiseptic, disinfectant** and **antiparasitic.** As an antiseptic it is superior to perchloride of mercury. It does not coagulate proteins, or form inert compound with tissues, possesses greater penetrating power and is more stable specially when iodide is added to the solution. On the skin it is an **irritant, rubefacient** and **vesicant** according to the strength and length of application. It stains the skin yellowish brown and deadens the cuticle which peels off. Owing to

the lasting irritation of the skin there is some congestion of the subcutaneous tissues which aids absorption of exudation.

Internally.—In the stomach and intestines iodine is slowly converted into iodide and absorbed as such, but much may be left free to cause vomiting, purging and colic. It therefore produces the usual effects of iodide. It is taken up by the spleen, lymphatic glands and to a less extent by the liver. It is excreted with the urine, milk, sweat and bronchial mucus. In poisoning, gastro-enteritis may cause death from collapse and failure of heart and respiration. In minute doses it occasionally stops vomiting.

Fresh thyroid contains 0.09 to 0.11 p.c. of iodine, while other tissues contain less than 0.001 p.c. Its supply is essential for the proper function of the gland. It exists in the thyroid gland as *thyroxine* (63 p.c.) and its deficiency either in the food or water favours development of hyperplasia. It has been shown that use of small amounts of iodine or iodides will prevent the occurrence of simple goitre in regions where it is endemic.

Acute toxic action.—It is generally taken in the form of tincture. Soon after swallowing there is uneasiness of the stomach with a disagreeable metallic taste followed by vomiting and severe abdominal pain. If the dose is large the pulse becomes feeble and collapse sets in. Diarrhoea follows, and the stool may contain blood. The vomit may be of iodine colour, and if the patient has taken starchy food, blue. Fatal cases are due to injection of too large quantities into serous cavities.

Treatment.—Evacuation. Demulcent drinks, chiefly starch, *e.g.* arrowroot or cooked flour. Eggs, milk and large quantities of alkalies in dilute solutions to fix the iodine. 5 p.c. solution of sodium thiosulphate may also be used. In poisoning due to injection into cysts, hydrocele, etc., very little can be done.

THERAPEUTICS

Externally.—Iodine is applied in subacute and chronic inflammation of joints, synovial membranes, lymphatic glands, pleura, etc. Its effects are mainly due to a mild irritant action which helps absorption of inflammation or exudation of underlying tissues or organs like other counter-irritants. Liquor iodi mitis has been successfully injected into cysts and hydroceles to induce an inflammation and adhesion of the walls and thus obliterate their cavities. Liquor iodi fortis being very strong cannot be painted more than twice or at the utmost thrice over the same spot. If the application causes much pain and irritation, the iodine can be washed off with alcohol, or with a solution of potassium iodide. It is used for the **sterilisation of the skin** before operations of all kinds when it penetrates readily into the pores and has a powerful germicidal action. Iodized phenol is a valuable local application in

endometritis. Being antiseptic, the mild liquor is painted over ringworm with benefit, though it causes some burning.

Internally.—Liquor iodi mitis painted over the gums and teeth dissolves tartar, heals ulcers, and stimulates the growth of gums, when they have ulcerated and receded. Iodine gargle (120 to 240 ms. of the mild liquor in water 8 oz.) checks mercurial salivation, and heals syphilitic and non-syphilitic sores of the mouth and throat. Pigmentum Iodi Co. is largely used in **tonsillitis** and in chronic granular pharyngitis. Liquor iodi mitis, 1 or 2 drops in 1 oz. of water, at times checks vomiting when given every fifteen minutes.

Iodine was used intravenously in various diseases, chiefly plague, erysipelas, septic wounds and other streptococcal infections. Its use as systemic anti-infective has been replaced by sulpha-drugs, penicillin and other antibiotics.

In the form of Lugol's solution (10 ms. three times a day in milk) it has been used in **exophthalmic goitre** apparently with some benefit. It improves nervousness, promotes sleep and appetite, slows the heart, and reduces the basal metabolism by 25 to 30 p. c. The results are not permanent for after a few weeks the symptoms return even though the treatment is continued. It is useful in that it makes the patient fit enough for surgical interference. In place of iodine, iodides may also be used. The relation of iodine in the formation of endemic goitre has led to the use of food rich in iodine, or iodised salt, as a prophylactic against the disease in endemic areas. But this treatment has been given up in favour of iodides and thyroid extract.

Radioactive iodine is rapidly absorbed from the stomach and can be detected in the human hand within 3 to 6 minutes. Its absorption is complete within three hours, and is distributed throughout the extracellular fluids. Since it is concentrated in the thyroid gland, it has been used to produce selective irradiation of the gland in **thyrotoxicosis** and has been found effective in number of cases by Hertz and Roberts and Chapman and Evans.* It is given by the mouth. It has also been used with some success in uncommon type of thyroid carcinoma in which iodine is concentrated by the neoplastic tissue.

Iodine compounds being opaque to X-rays have been used for purposes of diagnosis where bismuth or barium are inadmissible. The preparations used for the purpose are iodised oil (*see* page 344), iodophthalein (*see* page 384), and iodoxyl (*see* page 421).

IODOFORMUM. (Iodof.). CHI_3.—Iodoform may be obtained by the action of iodine on acetone in the presence of alkali.

* *Jour. Amer. Med. Assoc.*, 1946, 131.

Characters. Shining, lemon yellow, small hexagonal crystals, unctuous to the touch with a characteristic, persistent and disagreeable odour and taste. Volatilises slowly. *Solubility.*—Very slightly in water, in 8 parts of solvent ether, in 13 parts of chloroform, in 100 parts of alcohol (90 p.c.), fixed and volatile oils. Soluble in 7.5 parts of benzene.

Official Preparation

1. **Suppositoria Iodoformi.**—3 grs. or 0.2 grm. in each.

Non-official Preparations and Substitutes

1. **Collodium cum Iodoformo.**—Iodoform 1, Collodion 12. As a pigment in [illegible] *sores* and *glandular swellings*.

2. **Pigmentum Iodoformi Co., B.P.C.** *Syn.—Whitehead's Varnish.*—Contains iodoform 10, Sumatra benzoin 10, storax 7.5, balsam of tolu 5 and solvent ether to 100.

3. **Thymolis Iodidum.** *Syn.—Aristol.*—Prepared by the interaction of iodine and thymol. Contains 40 p.c. of iodine. A reddish-brown powder insoluble in water and glycerin, but soluble in collodion, ether and oils. Useful in *ulcerative lupus, tinea, psoriasis,* when applied as an ointment (10 p.c.), or dusted, or in collodion.

4. **Iodol.** *Syn.—Tetra-Iodo-Pyrrol.*—A brownish-white powder without disagreeable smell and toxic action, insoluble in water, but soluble 1 in 145 of glycerin, alcohol, chloroform, and ether. Externally it acts like iodoform, and internally like potassium iodide. *Dose.*—1 to 4 grs. or 0.06 to 0.25 grm. in pill or capsule.

5. **Calcii Iodobehenas, U.S.P.** *Syn.—Sajodin.*—An organic compound with calcium and iodine 23.5 p.c. *Dose.—U.S.P.*—7½ grs. or 0.5 grms.

Pharmacology

Externally.—Iodoform has no special action on the skin or mucous membrane, but in susceptible person it acts as an irritant and causes eruption to appear near the seat of the application. It is a local anaesthetic, antiseptic, disinfectant and deodorant. Pure dry iodoform is not an antiseptic and in solution it is very unstable. The antiseptic action is due to the formation of iodine which is slowly evolved when it comes in contact with tissues or their extracts, particularly with diseased tissues. The iodine is liberated in an amount which does not irritate the wound, but is sufficient to prevent the growth of micro-organisms.

Internally.—Iodoform is decomposed in the presence of alkaline fluids and in protein solutions, and the liberated iodine combines with the alkalies of the fluids to form iodides. After absorption iodine has been found in the saliva, sweat and bronchial secretions.

The symptoms of poisoning are complex and varied. A portion of iodoform circulates unchanged and gives rise to the cerebral symptoms; while other symptoms are due to the presence in the blood and tissues of iodine and iodides. The acceleration of the heart and other symptoms are due to the over-activity of the thyroid.

Toxic action.—Acute poisoning is rare. Chronic poisoning may take place either from repeated doses, or through absorption from a raw surface. The symptoms are malaise, vertigo, dilatation of the pupil, loss of appetite, gastro-intestinal disturbance, quick, feeble pulse, fever (temperature sometimes rising to 104°F.), delirium, mania, or melancholia, erythema and perhaps eczema (iodoform dermatitis), convulsion, collapse and at times death. Fatty degeneration of the liver and muscles, haematuria, and albuminuria sometimes occur. These symptoms may come on suddenly, or may develop gradually, lasting for weeks. Some are specially susceptible to iodoform.

Treatment of iodoform poisoning.—When slight, the symptoms disappear on withdrawal of the drug. In more serious cases the symptoms appear so late that removal of the poison will not avert a fatal result. Sodium bicarbonate grs. 15 every hour prevents the formation of free iodine. Milk of magnesia 60 ms. every three hours until bowels move should be given and then once every day to keep the intestines active. Potassium bromide grs. 20 in half a

tumbler of water followed by four 10 gr. doses hourly will antagonise cerebral excitement and help elimination.

THERAPEUTICS

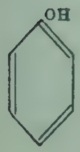
Externally.—Iodoform is employed as a local antiseptic, but the strong characteristic smell is the chief drawback to it use. It is used in surgery in various forms such as bismuth-iodoform-paste (*see* page 514), or as powder, ointment, emulsion, bougie, gauze, etc., in wounds, sloughing sores, syphilitic and scrofulous ulcers, chancres, abscess cavities, sinuses, fistulae, etc. Zinc-iodoform-paste (ZIPP) is safer and more effective than bismuth-iodoform-paste (see page 124). Collodion iodoform subdues mumps, buboes and chronic glandular enlargements. The suppository is used to relieve painful conditions of the bladder and rectum, and an ointment (1 in 10) gives great relief in **pruritus ani.** It may be insufflated (iodoform 2, starch 1) for otorrhoea and frequently proves extremely beneficial.

3. Coal-tar compounds

PHENOL

Phenol. C_6H_6O

Syn.—Acidum Carbolicum ; Carbolic Acid ; Phenyl Alcohol.
Source.—Obtained from coal-tar oil, or prepared synthetically.



Characters.—Small, colourless, needle-shaped, deliquescent crystals, or crystalline masses, becoming pinkish on keeping ; odour, peculiar, but not tarry ; taste, sweetish, pungent. *Solubility.*—1 in 13 of water, in glycerin, solvent ether, chloroform, fixed and volatile oils, and alcohol (90 p.c.).

OFFICIAL PREPARATIONS

1. **Glycerinum Phenolis.**—16 p.c. phenol.
2. **Suppositoria Phenolis.**—1 gr. (60 mg.) in each.
3. **Unguentum Phenolis.**—Phenol 3 p.c.

Phenol Liquefactum. (Phenol Liq.). **Syn.**—Acidum Carbolicum Liquefactum.—Liquefied Phenol contains phenol equivalent to 80.0 p.c. A colourless liquid, which may acquire a pinkish hue on keeping ; odour, characteristic and somewhat aromatic. Caustic.

OFFICIAL PREPARATION

1. **Trochisci Phenolis.**—Contains approximately 30 mg. or 1/2 gr. phenol in each.

NON-OFFICIAL PREPARATIONS

1. **Phenol cum Camphor, B. P. C.**—Phenol 1, Camphor 3. As a local anaesthetic for toothache.
2. **Phenol Iodisatum.** *Syn.—Iodised Phenol.*—Iodine 1, Liquefied Phenol 10.
3. **Auristillae Phenolis, B. P. C.**—Glycerin of phenol 180 ms., glycerin q.s. 1 oz.*
4. **Collutorium Phenolis Alkalinum, B. P. C.**—Liquefied phenol 15 ms., liq. pot. hydrox. 15 ms., solution of bordeaux B 5 ms., aqua q.s. 1 oz..

PHARMACOLOGY

Externally.—Pure phenol is an **irritant, anaesthetic** and **caustic.** Applied in the pure form on the skin or mucous membrane, it causes a sharp pain, followed by numbness and a white eschar without vesication. In dilute solution (3 to 4 p.c.) it is only mildly irritant but causes anaesthesia and is actively germicide. Phenol is

*Auristillae or ear-drops.

a protoplasmic poison and arrests the life-processes of the lower organisms, both vegetable and animal, and is a powerful parasiticide. It is a disinfectant, though not so powerful as corrosive sublimate and is also a deodorant. Coming in contact with the serum it precipitates proteins, and being rapidly soluble in lipoids it has a greater penetrating power than many other antiseptics. It is an efficient bactericide, and in concentrations varying from 1 in 30 to 1 in 200 it kills most bacteria. Spores are more resistant to its action, so that a 5 p. c. solution takes two days to kill the spores of anthrax. Since phenol has greater affinity for oil than for water or solutions of salts in the tissues, oily solutions are less antiseptic. On the other hand its activity is increased by the addition of sodium chloride which reduces its solubility and thus helps its concentration in the micro-organisms.

Internally. **Gastro-intestinal canal.**—In a concentrated form phenol has a similar action on the mucous membrane of the mouth, fauces, oesophagus and stomach, as on the skin. It is a powerful gastro-intestinal irritant. Since it is readily absorbed from the stomach and the intestine, it cannot act as an intestinal antiseptic. Unorganised or chemical ferments (*enzymes*), such as pepsin, ptyalin, are not so readily affected by it except in very large doses.

Blood and circulation.—Phenol increases the rate of the heart, due probably to direct action on the cardiac muscle or on the nerves. The heart is subsequently slowed. Injected directly into the blood it depresses the vasomotor centre. This effect combined with the weakness and slowness of the heart causes the blood pressure to fall. Although phenol added to defibrinated blood leads to the slow formation of methaemoglobin, this change does not occur in the living animal.

Respiration.—Respiration is not affected in small doses, but large doses first stimulate then paralyse the respiratory centre making the respiration slow and shallow.

Temperature.—No effect is produced by medicinal doses but large ones lower it, possibly due to collapse. It is not certain whether the fall of temperature is aided by some changes in the regulating mechanism.

Nervous system.—In fairly large doses it affects the medulla and cerebrum. It also stimulates the salivary and sweat centres, producing salivation and perspiration. The cells of the anterior cornua are first stimulated then paralysed, the result being convulsion followed by paralysis. Poisonous doses produce headache, giddiness, contracted pupils and finally coma.

Urine.—Phenol is chiefly excreted by the urine in the form of pyrocatechin and hydroquinone which are oxidised as coloured substances and the urine assumes a *dark* or

olive-green colour. The unoxidised portion combines with sulphuric acid and excreted as phenyl sulphuric acid which is inert. Sometimes albumin is detected. *In poisoning by phenol, the normal sulphates disappear from the urine.* The glycuronates reduce Fehling's solution and the urine therefore gives rise to the suspicion of diabetes. The urine in these cases resists decomposition for a considerable time.

Elimination.—By the saliva, sweat, respiratory and gastro-intestinal secretions and urine. A portion is lost in the body.

Acute toxic action.—If swallowed in a concentrated form the patient feels intense burning pain in the mouth, fauces and stomach, with the formation of white eschars in the mouth, etc. He soon becomes collapsed with a cold clammy sweat, subnormal temperature, weak, feeble pulse, and shallow laboured breathing, heart and respiration stopping almost simultaneously. Reflex excitability is lost and convulsions occasionally set in. Urine becomes dark green, and finally the patient becomes insensible and comatose. Small doses cause nephritis with albumin in the urine. The *post-mortem* reveals hard, white eschars in the mouth, oesophagus and stomach with or without inflammatory redness. Blood becomes dark and its coagulability is diminished.

Treatment.—Pump, emetics. Wash out the stomach with warm water, better with olive oil, a quantity of the oil being left in the stomach. If coma sets in, artificial respiration, caffeine and strychnine to sustain the heart. Chalk, saccharated lime, egg albumin, oils, demulcents, stimulants, hot water bottle, etc., are useful adjuvants.

Caution.—Green or smoky urine is often the first warning but in doubtful cases the urine should be examined to ascertain the presence or absence of ordinary sulphates. The products of carbolic acid in the urine can be detected by distilling the urine, and adding bromine water to the distillate, when white crystalline sulphocarbolate precipitates.

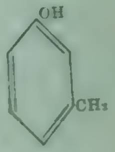
THERAPEUTICS

Externally.—Crude phenol is employed to disinfect and remove the foul odours of water-closets, drains, hospital wards, bed-pans, etc. To stimulate indolent sores, to prevent the foul smell of gangrenous ulcers, to destroy exuberant granulations, condylomas and the poison of poisoned wounds, the application of undiluted phenol is most valuable. To wash surgeon's hands, instruments, sponges, linen, and parts to be operated upon, carbolised lotions were extensively used in surgical practice, but its use has become very much restricted in recent years. Undiluted liquefied phenol has been used by injection as a sclerosing agent in varicose veins and piles. The application of phenol camphor or iodised phenol relieves excoriation and ulceration of the os and cervix and chronic endometritis. A vaginal douche (1 in 80 or 100) is beneficial in leucorrhoea, uterine ulcers and cancer, but it sometimes causes itching and irritation.

Internally.—For ulcerative and aphthous stomatitis, follicular tonsillitis and diphtheria the glycerin may be

used as a paint, or a lotion (glycerin. phenolis 15 to 20 ms. in water 1 oz.) may be used as a gargle.

CRESOL.—Cresol. Syn.—Acidum Cresylicum ; Cresyl Hydrate.
Source.—A mixture of cresols and other phenols, obtained from coal-tar.

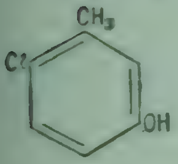


Characters.—An almost colourless to pale brownish-yellow liquid, becoming darker on keeping, or on exposure to light. *Soluble* in 50 parts of water, solution being neutral, freely soluble in alcohol (90 p.c.), in solvent ether, chloroform, glycerin and in the fixed and volatile oils.

Official Preparation

1. **Liquor Cresolis Saponatus.** *Syn.—Lysol.*—50 p.c.

Chlorocresol. Syn.—*Para*chloro*meta*cresol.—Chlorocresol is 6-chloro-3-hydroxytoluene and may be prepared by the chlorination of *m*-cresol.



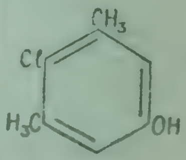
Characters.—Colourless crystals ; odour, characteristic. *Soluble* in 250 parts of water ; more soluble in hot water ; readily soluble, in alcohol (90 p.c.), in solvent ether, in terpenes, in fixed oils, and in solution of sodium hydroxide. Volatile in steam.

Pharmacology and Therapeutics

Cresol is less poisonous and less toxic but more efficient germicide than phenol, and may be used in the form of lotions and ointments in its place. It is chiefly used as a surgical disinfectant for the purpose of sterilising instruments and for washing wounds. A 2 p. c. solution may be used for washing hands and the liquor diluted 1 in 500 may be used as douche in obstetrical and gynaecological practice. In the form of vapour it is used in whooping-cough, and other respiratory troubles, the atmosphere of the room being rendered saturated with the vapour. It is a cheap and powerful disinfectant, less poisonous than both phenol and mercurials and therefore more suitable for general use, but loses 50 to 70 p. c. of its power when it comes in contact with organic matter.

Chlorocresol is a more powerful bactericide. about ten times more powerful than phenol, with relatively low toxicity. It is largely used as a preservative specially for hypodermic injections. It may be used both in acid and alkaline solutions though less active in the latter medium.

CHLOROXYLENOL. Syn.—*Para*chloro*meta*xylenol.—Chloroxylenol is 2-chloro-5-hydroxy-1 : 3-dimethylbenzene.



Characters.—White to creamy white crystals, or a crystalline powder ; odour, characteristic. *Soluble* in about 3000 parts of water ; more soluble in hot water ; soluble in alcohol (90 p.c.), in solvent ether, in benzene and in solutions of alkali hydroxides. Volatile in steam.

Official Preparation

1. **Liquor Chloroxylenolis.** *Syn.—Roxenol.*—A yellow or amber coloured liquid, soapy to the touch, and odour of terpineol.

Acidum Ricinoleicum. (Acid. Ricinoleic.).—Ricinoleic Acid is a mixture of fatty acids obtained by the hydrolysis of castor oil.

Characters.—A yellow or yellowish-brown, viscous liquid; odour and taste characteristic. [illegible] in water; soluble in alcohol (90 p.c.) and in solvent ether.

ACTION AND USES.—Chloroxylenol is an antiseptic and bacteriostatic of low toxicity. It has a pleasant odour and is largely used in the form of the liquor for wounds and abrasions, as a **mouth wash** (10 to 30 ms. in a tumblerful of water) and as a **vaginal douche** (3 drs. in a pint of warm water). The advantage claimed for chloroxylenol over cresol is that it is not irritant.

Ricinoleic acid forms soap with alkalies and organic bases which has greater bactericidal properties and is therefore used in the preparation of Liq. Chloroxylenolis.

RESORCINOL. (Resorcin.). Syn.—Resorcin.

Source.—Resorcinol is *m*-dihydroxybenzene and may be obtained by the interaction of sodium hydroxide and sodium *m*-benzene-disulphonate.

Characters.—Colourless, or nearly colourless, acicular crystals or powder. Faint odour; taste, pungent and sweetish, followed by bitterness. *Solubility.*—In less than 1 part of water, in 1 part of alcohol (90 p.c.), in solvent ether, glycerin, and olive oil.

NON-OFFICIAL PREPARATIONS

1. **Auristillae Resorcinolis. B. P. C.**—Resorcinol 4 grs., alcohol (95 p.c.) 360 ms., aqua q.s. 1 oz.
2. **Pasta Resorcinolis Co., B. P. C.** *Syn.*—*Lassar's Stronger Paste of Resorcin.*—Resorcin, zinc oxide, starch, each 2 grms., liquid paraffin, q.s. 8 grm.
3. **Pasta Resorcinolis et Sulphuris, B. P. C.**—Resorcin and precipitated sulphur each 1/2 oz., zinc oxide 3 oz., emulsifying ointment 4 oz.

ACTION AND USES

Resorcin is an **antiseptic, antipruritic and parasiticide.** As an antiseptic it is stronger than phenol but less poisonous. Its most important use is in the treatment of **skin diseases** either as an ointment (20 grs. to 1 oz.) or as a lotion. In 1 or 2 p.c. solution it is antipruritic and antiseptic and may be used in **eczema, urticaria,** and other irritable skin affections. Stronger solution (3 to 4 p.c.) is actively stimulating and keratolytic and is useful in **seborrhoea, acne vulgaris, psoriasis, alopecia,** etc. With glycerin it is useful as a paint in sore-throat *. As a lotion it is valuable in dandruff. †

Internally.—It acts as an intestinal antiseptic but is seldom used as such.

TRINITROPHENOL, B. P. C. (Trinitrophen.). Trinitrophenol. Syn.—Picric Acid.

Source.—Obtained by treating phenol with sulphuric acid at a suitable temperature, and by treating the product with nitric acid. Contains not less than 99 p. c. of $C_6H_3O_7N_3$.

Characters.—Bright yellow, crystalline powder. Inodorous; taste, very bitter. Explodes when heated rapidly, or subjected to percussion. *Solubility.*—In 90 parts of water and in about 12 parts of alcohol (90 p.c.).

NON-OFFICIAL PREPARATION

1. **Unguentum Trinitrophenolis.**—Picric acid 2, water 2, soft paraffin 96.

ACTION AND USES

Trinitrophenol is an irritant to the skin and mucous membranes. In large doses it causes vomiting and often anuria and strangury. After absorption it colours the skin and mucous surfaces yellow.

*Resorcin.	grs. 15
Glycer. Boracis	oz. 1

† Resorcin.	grs. [illegible]
Hydrarg. perchlor.	gr. [illegible]
Sp. ether.	ms. [illegible]
Ol. arachis.	ms. [illegible]
Ol. lavand	ms. [illegible]
Aq. [illegible] flor.	ad. oz. [illegible]

[illegible] jaundice, due to the staining of the epithelium by the acid. The saturated solution is used as a hardening agent in microscopical work. When heated with glucose it is reduced to picramic acid and this test is utilised in the detection and estimation of glucose in urine (Johnson's test); with citric acid it forms the well-known Esbach's test for albumin in urine.

It is a protoplasmic poison and precipitates proteins and acts as an antiseptic and is four times more active than phenol. Its chief therapeutic use is in cases of **burns** and **scalds**. Lint or cotton-wool soaked in 1 p.c. solution of the acid is generally used for the purpose. A 5 p.c. solution in alcohol hardens the skin and checks local sweating. The ointment may be used in eczema, pruritus, etc.

The stains are removed by first applying powdered potassium sulphate for a minute and then washing with soap.

PIX CARBONIS PRAEPARATA. (Pix Carb. Praep.). **Syn.**—[illegible] Beng.—Prepared Coal Tar is obtained by heating commercial coal tar in a shallow vessel for one hour at 50°C.

Characters.—A nearly black, viscous liquid, brown in very thin layers; heavier than water. [illegible] empyreumatic odour. Almost entirely soluble in benzene [illegible] chloroform; partially in alcohol (90 p.c.), and in solvent ether; almost insoluble in water.

Composition.—(1) *Benzene and homologous hydrocarbons.* (2) *Phenol.* (3) [illegible] *naphthalene, anthracene, etc.*

OFFICIAL PREPARATION

1. **Liquor Picis Carbonis.**—20 p.c. It is the official imitation of **Liquor Carbonis Detergens** which is an alcoholic solution of common coal tar.

ACTION AND USES.—Coal tar is used in place of wood tar for external application with this advantage that it is less irritant and less liable to produce any toxic manifestation after absorption. It is used to relieve itching and inflammation of eczema, prurigo, etc. It should not be used when the skin is infected with pyogenic [illegible]. An ointment* or a lotion (5 to 15 p.c.) is valuable in chronic eczema.

Pix Liquida. (Pix Liq.). Tar. **Syn.**—Wood Tar; Pix Pini, U.S.P.; Pine Tar; Stockholm Tar.

Source.—A bituminous liquid, obtained from the wood of various trees of the family *Pinaceae* by destructive distillation.

Characters.—A dark brown or nearly black semi-liquid substance. Odour, [illegible] empyreumatic taste; heavier than water. *Solubility.*—In alcohol (90 p.c.), in solvent ether and in fixed and volatile oils.

Composition.—(1) *Cresol.* (2) *Phenol.* (3) *Guaiacol.* (4) *Pyrocatechol.* (5) [illegible] (6) *Xylol.* (7) *Acetone.* (8) *Resins, etc.*

NON-OFFICIAL PREPARATIONS

1. **Syrupus Picis Liquidae, B.P.C.**—Tar 5.5 grms., sugar 850 grms., alcohol [illegible] 11.5 mils, water to 1000 mils. Used in winter cough, phthisis and chronic bronchitis. *Dose.*—1 to 2 drs. or 4 to 8 mils.

2. **Unguentum Picis Pini, U.S.P.**—Tar 50, yellow wax 15, yellow ointment 35.

ACTION AND USES

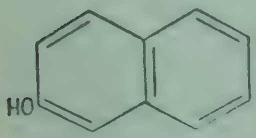
Externally.—Wood tar owes its property to the presence of phenol-like bodies and is an antiseptic and **vascular stimulant.** It is sedative to the nerves. The ointment is an excellent application in chronic scaly skin diseases, such as psoriasis. Chronic eczema is benefited by it.

Internally.—It may cause indigestion, and in large doses symptoms of carbolic acid poisoning. It is absorbed and during elimination exerts a beneficial influence on the bronchial mucous membrane, stimulating, deodorising and checking profuse secretion, and promot-

*Liq. picis carb.	ms. 20
Liq. plumb. subacet. fort.	ms. 20
Hydrarg. ammon.	grs. 15
Paraff. moll. alb.	oz. 1

ing free expectoration. It is therefore used in chronic bronchitis, bronchiectasis and winter cough. It may be given in the form of syrup. Apomorphine combined with syrup of tar and syrup of virginian prune makes an admirable cough linctus. (*See* page 338).

BETANAPHTHOL. (Betanaph.). $C_{10}H_7OH$. **Syn.**—Naphthol.



Source.—Betanaphthol is ß-hydroxynaphthalene and may be obtained by the fusion of sodium naphthalene-ß-sulphonate with sodium hydroxide.

Characters.—White, or nearly white, crystalline lamellae, or powder, with odour resembling phenol and pungent taste. *Solubility.*—1 in 1000 of *cold* water, 1 in 2 parts of alcohol (90 p.c.), in solvent ether, in olive oil and glycerin.

Incompatibles.—Camphor, ferric chloride, menthol, phenazone, and phenol.

B. P. Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

PHARMACOLOGY AND THERAPEUTICS

Betanaphthol is a powerful antiseptic and disinfectant, stronger than phenol but is not so corrosive. Naphthols irritate the mucous membrane, and when inhaled cause sneezing and coughing. They are excreted in the urine in combination with glycuronic and sulphuric acids, which give the urine a reddish-brown colour. During the course of excretion they cause pain in the bladder and urethra with strangury and swelling of the mucous membrane. It is widely used in various skin disease as an ointment (1/2 to 5 p.c.) such as **favus, scabies, ringworm,** etc. A 10 p.c. ointment, either alone or with sulphur, is useful **in psoriasis.**

Internally it is chiefly used as a gastro-intestinal antiseptic in diarrhoea and typhoid diarrhoea. It may be given in *cachets* or *pills*, or as an *emulsion*. The pills may be coated with keratin.

In 15 gr. doses given every hour for three doses betanaphthol is an anthelmintic for *ankylostomum duodenale* and is preferable to thymol, being less irritating and cheaper. For method of administration see page 390. Both these drugs have however been replaced by other anthelmintics (see page 394).

The use of naphthols should be avoided in irritation of the bladder, kidneys and urethra.

Salol, B.P.C.—Salol. $C_{13}H_{10}O_3$. **Syn.**—Phenyl Salicylate.

Source.—By the interaction of salicylic acid and phenol.

Characters.—Colourless crystals, with a faint aromatic odour and slight taste. *Solubility.*—Almost insoluble in water, soluble in 15 parts of alcohol (90 p.c.) and in fixed and volatile oils.

Dose.—5 to 20 grs. or 0.3 to 1.2 grms.

ACTION AND USES.—Salol has no action on the stomach but splits up in the intestine by the fat-splitting ferment of the pancreatic juice into salicylic and carbolic acids which act as antiseptics and are then absorbed producing the usual effects. In large doses it is apt to cause *carboluria* and it should not, therefore, be given in too large doses, or for too long a period continuously, or to persons suffering from renal disease. It is used to coat pills not intended to be dissolved in the stomach.

Coal-tar Dyes

These are classified as follows :—

1. Acridine Dyes : **Acriflavine, Proflavine, Aminacrine.**
2. Azo Dyes : **Scarlet Red, Congo Red** (*see* p. 671), **Pyridium** (*see* p. 417).
3. Triphenylamine Dyes : **Crystal Violet, Brilliant Green, Malachite Green.**
4. Fluorescein Dyes : **Soluble Fluorescein, Mercurochrome** (*see* p. 504).
5. Phenolphthalein Dyes : **Iodophthaleinum** (*see* p. 384).
6. Miscellaneous Dyes : **Methylene Blue, Indicarminum** (*see* p. 422).

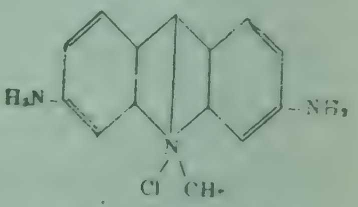
ACRIFLAVINA

(Acriflavin.). $C_{14}H_{14}N_3Cl,HCl$

Source.—Acriflavine is a mixture of the hydrochlorides of 2 : 8-diamino-10-methylacridinium chloride and 2 : 8-diaminoacridine, and contains approximately one-third of its weight of diaminoacridine dihydrochloride.

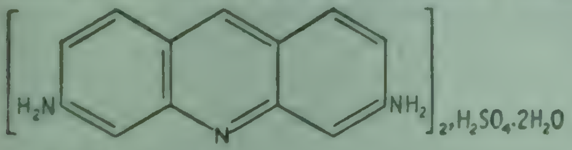
Characters.—An orange-red to red, crystalline powder ; odourless ; taste, acid. *Soluble* in 3 parts of water, may be precipitated by dilution, or on standing ; in 500 parts of normal saline solution, in alcohol (90 p.c.), and in glycerin. Almost insoluble in solvent ether, in chloroform, in fixed and volatile oils and in liquid paraffin.

Incompatibles.—Chlorine antiseptics, **phenol and corrosive sublimate.**



PROFLAVINAE HEMISULPHAS. (Proflav. Hemisulph.). Syn. —Neutral Proflavine Sulphate ; Proflavine.—Proflavine Hemisulphate is the neutral sulphate of 2 : 8-diaminoacridine.

Characters.—An orange to red, hygroscopic, crystalline powder ; odourless ; **taste, bitter. *Soluble* in 150 parts of water, in 1 part of boiling water, in 32 parts of glycerin, very slightly soluble in alcohol (90 p.c.) ; insoluble in solvent ether and in chloroform.**



$(C_{13}H_{11}N_3)_2,H_2SO_4,2H_2O$

AMINACRINAE HYDROCHLORIDUM. (Aminacrin. Hydrochlor.).—Aminacrine Hydrochloride is 5-aminoacridine hydrochloride monohydrate. Prepared by treating *N*-phenylanthranilic acid with phosphorus oxychloride and treating the product with ammonium carbonate in phenol.

Characters.—A pale yellow, crystalline, odourless powder ; taste, bitter. *Soluble* in 300 parts of water ; in alcohol (90 p.c.) ; in glycerin ; insoluble in solvent ether ; in chloroform.

Euflavina, B.P.C. Syn.—Neutral Acriflavine.—It is a mixture of 2-8-diamino-10-methylacridinum chloride and 2 : 8-diaminoacridine monohydrochloride, containing approximately one-third of its weight of the latter.

Characters.—An orange-red or brownish-red powder ; odour, faint ; taste, very bitter. Slightly soluble in cold water ; more in warm water, slightly soluble in alcohol.

PHARMACOLOGY AND THERAPEUTICS

Acriflavine, proflavine hemisulphate, euflavine and aminacrine hydrochloride are all derivatives of acridine and are used as powerful **antiseptics** against gram-negative bacteria. They do not irritate tissues, stimulate granulating process, are active in the presence of serum and do not interfere with phagocytosis. Acriflavine is

used in modern surgical practice as a lotion, ointment or gauze, for sores, ulcers, abscess cavities, etc. The best method is to wash out with a solution (1 in 1000 of normal saline) and then to pack with gauze steeped in the solution. In combination with tannic acid, it is used in the treatment of burns and scalds. A neutral solution, 1 in 4000 of saline has been used as a bowel wash in ulcerative colitis, and as urethral irrigation (1 in 4000) in gonorrhoea. It is also useful in gonorrhoeal infection of women. The method is to take a douche, and then lying down inject 25 mils (6 drs.) of 1 in 1500 to 1 in 500 solution and retain for half an hour. This may be done twice a day.

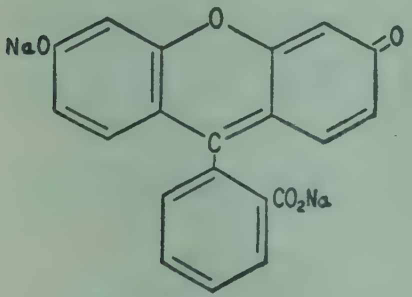
Solution of acriflavine 1 in 1000 dropped into the eye and followed by wet dressing of strong solution of magnesium sulphate and sodium chloride is valuable in gonorrhoeal ophthalmia while a solution of 1 in 4000 is useful in conjunctivitis.

Proflavine resembles acriflavine but is less toxic and less irritant and is bactericidal in the presence of serum.

Proflavine combined with sulphathiazole in equimolecular proportions, is non-irritant unless used in excess, and has a wide range of bacteriostatic activity and can be dusted over wounds. It is highly effective against both gram-positive and gram-negative organisms.

The bacteriostatic and bactericidal properties of aminacrine are slightly greater than proflavine. When injected into mice its toxicity is midway between that of proflavine and acriflavine. Irrigation with 1 in 1000 solution of aminacrine hydrochloride controls sepsis in wounds, specially against haemolytic staphylococci. 1 p.c. solution in 5 p.c. alcohol effectively sterilises the skin prior to operation.

FLUORESCEINUM SODIUM.—(Fluoresc. Sod.). **Syn.**—Soluble Fluorescein. $C_{20}H_{10}O_5Na_2$.



Source and Characters.—Fluorescein Sodium is the di-sodium salt of fluorescein. Prepared by the condensation of resorcinol and phthalic anhydride. An orange-red powder ; odourless ; almost tasteless. *Soluble* in 1 part of water, and in 5 parts of alcohol (90 p. c.).

ACTION AND USES

Flurorescein is used as a diagnostic agent in various ophthalmic and circulatory conditions. A 2 p.c. solution of flourescein with 3 p.c. of bicarbonate of soda is used to diagnose corneal ulcers and abrasions. The eye should be cocainised before applying fluorescein. It does not stain the healthy tissue but produces a green stain when the dye penetrates any abrasion or ulcer on the eye. Similarly loss of substance in the conjunctiva produces a yellow stain. May be given by the mouth in 3 to 6 grm. doses, when it causes a yellow discolouration of the whole body which disappears in 24 hours ; the normal eye is

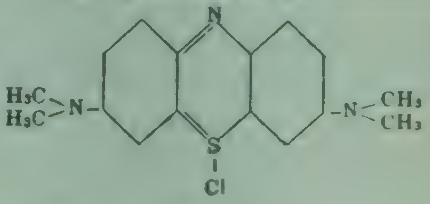
not coloured, but in intra-ocular disease, glaucoma or iritis, the aqueous humour is coloured green in about 20 minutes, while the conjunctiva remains unaffected.

Its use has been advocated as a test for the condition of the circulation of an extremity. For this purpose a solution containing 10 mils of 5 p.c. fluorescein and 5 p.c. of bicarbonate of soda is administered intravenously and the patient is kept in a dark room under an ultra-violet light. Amount of dye seen in the tissues depends upon the amount of blood flow. Dead tissues do not show any colour. The test is unreliable in pigmented areas. While excreted in the urine it makes it grass-green fluorescent.

Since fluorescein is concentrated in malignant tumour tissue, irradiated sodium fluorescein and other fluorescent salts have been used in the treatment of **carcinomatous growths.*** A 2 to 2.5 p.c. solution of the sodium salt is painted over the affected area and part of the apparently healthy skin surrounding the growth, for two or three times, and then irradiated by X-ray or radium of moderate penetration. In deep-seated growths it is given internally or intravenously before irradiation. The dose *per os* is 2 grms. in capsules, or cachets of 1 grm. each. Combined with radioactive iodine fluorescein has been used intravenously for **diagnosis and localisation of brain tumour.**

METHYLTHIONINAE CHLORIDUM. (Methylthionin. Chlor.). Methylene Blue. $C_{16}H_{18}N_3ClS, 3H_2O$.

Source.—It is tetramethylthionine chloride. May be prepared by the interaction of dimethyl-*p*-phenylenediamine with thiosulphuric acid, and subsequent oxidation. Contains not less than 80 p.c. of methylene blue.



Characters.—A dark greenish, crystalline powder with a metallic lustre, or a dull, dark-green or brown powder. Almost odourless. *Soluble* in water, in alcohol (90 p.c.) and in chloroform.

B. P. Dose.—1 to 5 grs. or 60 to 300 mg.

Pharmacology and Therapeutics

Externally.—Methylene blue was the first of the antiseptic dyes to be used but its bactericidal properties are mild. A 3 p.c. solution is useful in tropical ulcer and as a local application for eczema in children; after application it is allowed to dry and then covered with a thin layer of collodion. A lotion (1 in 5000 to 1 in 1000) is useful as a bowel wash in dysentery and ulcerative colitis.

Internally.—Since it is excreted by the kidneys it was used to disinfect the urinary tract but its place has been taken up by more efficient bactericidal agents.

It has been used in the treatment of **cyanide poisoning** and 50 to 100 mils (1½ to 3 ozs.) of 1 p.c. solution has been used intravenously. The action is due to the formation of methaemoglobin which binds the cyanide as the stable non-toxic cyanmethaemoglobin. Others however believe that it acts by its intracellular oxidative function. It is also used to relieve **sulphonamide cyanosis** in 1 to 2 gr. doses by the mouth or in urgent cases 10 to 20 mils of 1 p.c. solution intravenously (*see* page 558).

* Copeman, Coke and Gouldesbrough, *B.M.J.* 1929.

After its ingestion by the mouth it is found in large quantities in the bile, and is excreted in the urine colouring it bluish green. It has therefore been used to test the liver efficiency and the function of the kidneys. For the former 2 mg. is given before breakfast and the urine tested every 4 hours for 12 hours. If the liver is deficient the urine will become green from 5th to 9th hour. For testing renal function, 1 mil of a 5 p. c. solution is injected into the gluteal muscle and within 10 to 15 minutes blue jets of coloured urine should escape through the ureteral openings when observed under cystoscope. The test has been given up in favour of indigo carmine (*see* page 422).

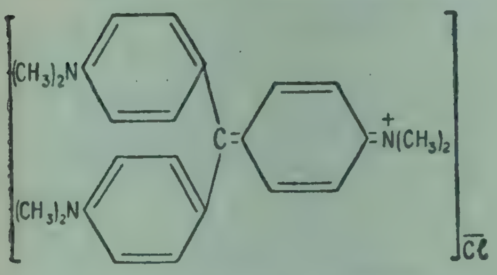
As it is eliminated by the gall-bladder it has been used with some success in ½ to ¾ gr. (30 to 50 mg.) doses in cholangitis and cholecystitis.

The usual method of administration is in cachets or capsules. The solution for injection should be sterilised by heating in an autoclave or by tyndallisation.

Except slight vesical or gastro-intestinal irritation no untoward effects are observed with therapeutic doses, even after prolonged use. If it is rapidly absorbed in considerable amounts, symptoms of poisoning may appear showing signs of paralysis of the heart and respiratory centres.

VIOLA CRYSTALLINA. (Viola Crys.). **Syn.**—Medicinal Gentian Violet; Methylrosaniline Chloride. (*See* page 397).

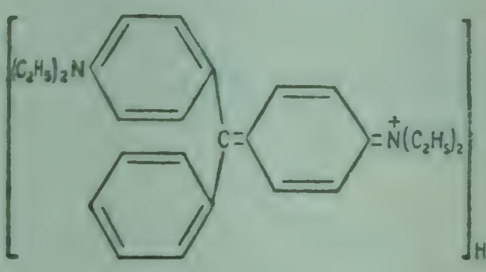
ACTION AND USES.—It is a powerful **bactericide** for gram-positive organisms, specially, staphylococci. It is largely, used as an anthelmintic (*see* page 397) and in various skin diseases and burns. A 2 to 5 p.c. solution is a valuable application in **eczemoid ringworm, intertrigo, seborrhoeic dermatitis** and **impetigo.** It is best applied once or twice daily after making the surface free from crusts and drier if oozing. Because of its analgesic and antiseptic action it is used in burns in place of tannic acid as the crust formed is more flexible. It may be used in the form of spray (2 p.c. aqueous solution), till a crust is formed, or as a jelly (2 p.c.) either alone or the following* may be combined with tannic acid jelly. It is now combined with brilliant green and acriflavine as a "triple dye" mixture. This forms a stable solution, relieves pain and obviates the preliminary cleansing which is so painful in extreme burns. The usual formula is aqueous solution of gentian violet, 1 p.c.; aqueous solution of brilliant green, 1 p.c.; neutral acriflavine solution, 0.1 p.c. Blisters should be cut and dead tissues removed, but no other preliminary cleaning-up is necessary. Another formula is gentian



*Gentian violet 1 p.c., quinin. urea hydrochlor. 0.5 p.c., glycerin. trag. base (powdered trag. 2 p.c., glycerin 10 p.c. water to 100).

violet 1 p.c., brilliant green 0.1 p.c., acriflavine 0.1 p.c., to which 5 p.c. sulphadiazine is added. This is applied in the form of a jelly. It is painless, soothing and no covering is required.

VIRIDE NITENS. (Virid. Nit.).—Brilliant Green is the sulphate of di-(*p*-diethylamino)-triphenyl-carbinol anhydride. Small, glistening, golden crystals. *Soluble* in water, and in alcohol (90 p.c.).



ACTION AND USES.—Brilliant green is used as a surgical antiseptic as a 0.05 to 0.1 p.c. solution in water or hypertonic saline. It not only acts as an antiseptic but encourages epithelization. Its uses are very similar to gentian violet and as mentioned above it is used in combination with acriflavine and gentian violet in the treatment of burns. It has given very good result in the treatment of sycosis. The crusts and scales are first removed with a 5 p.c. salicylic acid ointment, and the loose hairs epilated. The area is painted daily or on alternate days with a 1 p.c. solution in 70 p.c. alcohol.

NON-OFFICIAL PREPARATIONS

1. **Viride Malachitum, B.P.C.** *Syn.—Malachite Green; Benzaldehyde Green.*—It is oxalate of *pp'*-tetra-methyldiaminotriphenylcarbinol. A solution 1 in 2000 kills *Staphylococcus aureus* in serum, and 1 in 5000 kills spores of *B. subtilis.* Much used as an *antiseptic wound dressing.* Used in 1 per cent. solution in mycotic disease of the skin.

2. **Rubrum Scarlatinum, B. P. C.** *Syn.—Scarlet Red.*—An azo-colouring matter of the secondary diazo group. Insoluble in water, more soluble in alcohol, and readily soluble in chloroform, oils and warm petroleum preparations. Promotes the growth of epithelium in the treatment of wounds, burns, and ulcers. Used as a dusting powder with boric acid, or as an ointment from 1 to 8 p.c.

4. Quaternary Ammonium Compounds

CETRIMIDUM. Syn.—Cetavlon.—Cetrimide is a mixture of alkyl ammonium bromides prepared by condensation of technical cetyl bromide with trimethylamine. A white to creamy-white, voluminous, free-flowing powder : odour, characteristic and faint ; taste, bitter and soapy. Soluble in about 10 parts of water ; almost completely soluble in alcohol (90 p.c.).

ACTION AND USES.—This group of antiseptics besides being **antibacterial** are also **detergent.** In this group the hydrogen atoms of ammonium-ion are replaced by various organic radicals. While they possess high bactericidal powers against certain species of bacteria there is a wide variation in the efficiency for different species. Their efficacy is lessened by certain organic matters including soap and pus. Their characteristic property is that when applied to the skin they form a tough but thin film on the skin.

Cetrimide solution is used for the purpose of (*a*) **sterilising the skin** and hands. It is an efficient preparation in the pre-operative wash-up of the surgeon's hands ; (*b*) cleansing and disinfecting wounds. It removes contaminating matter from wounds, burns and abrasions quickly and is non-irritant ; (*c*) removing scabs and crusts easily without rubbing ; (*d*) disinfection of infected articles, like plates and cups, instruments, etc. For this purpose 1 p.c. solution is used.

5. Miscellaneous compounds

LIQUOR FORMALDEHYDI

(Liq. Formaldehyd.). CH_2O

Syn.—Formalin ; Formol.

Source.—Solution of Formaldehyde is an aqueous solution of formaldehyde, with a variable amount of ethyl alcohol or methyl alcohol, or both. Contains 37 to 41 p.c. w/v of CH_2O.

Characters.—A colourless liquid with a characteristic pungent odour. Freely soluble in water, and in alcohol (90 p.c.).

Dispensing hints.—It should be kept in well-stoppered bottles, in a moderately warm place.

PHARMACOLOGY AND THERAPEUTICS

Formalin is a **caustic.** When diluted with ten times its bulk of water it is useful as a hardening histological agent or as a preservative for museum specimens. The solution is a powerful germicide and in dilutions of 1 in 200 kills most micro-organisms. It possibly acts by combining with some amino-group in the protein molecule. Being a powerful antiseptic, it is used for sterilising instruments, and for preservation of corpses for dissection, but on account of its necrotic action on the skin it is not suitable for treatment of wounds. It causes soft corns to shrivel up.

A 0.5 to 1 per cent. solution may be used as an antiseptic gargle or mouth-wash in stomatitis, and is useful as a spray in diphtheria and whooping-cough. A 30 p.c. solution in glycerin makes an excellent pigment in ringworm and parasitic skin diseases.

Formaldehyde 1, chloroform 1 and alcohol 2 is recommended as an antiseptic inhalation in phthisis ; 5 to 10 drops being sprinkled on cotton-wool, or inhaled from the pad of an oro-nasal inhaler.

It may be used as a spray to disinfect infected rooms, or may be used as a gaseous disinfectant either by using paraform tablets or by generating the gas by adding potassium permanganate to the solution. *Paraform* requires a special apparatus, which is known as "Formogene" or "Alformant" lamp. The vapour thus produced disinfects surface only. It does not bleach fabrics.

Formaldehyde solution is **incompatible** with ammonia and all oxidising substances and renders gelatin insoluble.

ACIDUM BORICUM

(Acid. Boric.). H_3BO_3

Syn.—Boracic Acid.

Source.—Boric Acid may be obtained by the interaction of sulphuric acid and native borates.

Characters.—White crystals, or powder : unctuous to touch. Odourless. Taste, slightly acid and bitter. *Solubility.*—1 in 25 of water ; 1 in 4 of glycerin, 1 in 30 of alcohol (90 p.c.).

B. P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

Enters into.—Cataplasma Kaolini and Liq. Sod. Chlorinat. Chir.

OFFICIAL PREPARATIONS

1. **Glycerinum Acidi Borici.** *Syn.—Glycerite of Boroglycerin.*—31 p.c.
2. **Unguentum Acidi Borici.**—Boric acid 1 p. c.

BORAX.—Borax. $Na_2B_4O_7.10H_2O$. Syn.—Borax Purificatus; Sodium Borate. *Shohaga*, Beng., Hind.

Source.—Obtained from native borax, or by boiling native calcium borates with solution of sodium carbonate. Contains 99 to 103 p.c. of sodium borate.

Characters.—Transparent, colourless crystals, or a white powder; odourless; taste saline and alkaline. Effloresces in dry air, and, on ignition, loses all of its water of crystallisation. *Soluble* in 25 parts of water; insoluble in alcohol (90 p.c.), soluble in 1 part of glycerin.

Incompatibles.—Mineral acids, most metallic salts, mucilage of acacia also alkaloidal salts.

B. P. Dose.—5 to 15 grs. or 0.3 to 1 grm.

OFFICIAL PREPARATION

1. **Glycerinum Boracis.**—12 p.c.

NON-OFFICIAL PREPARATIONS

1. **Auristillae Acidi Borici, B. P. C.** *Syn.—Boric Acid Ear Drops.*—Boric acid [illegible] gr., alcohol (95 p.c.) 100 ms., aqua q.s. 1 oz.
2. **Collunarium Alkalinum, B. P. C.** *Syn.—Alkaline Nasal Wash.*—Sod. bicarb. [illegible] gr., borax [illegible] gr., liquefied phenol 25 ms., sucrose 100 gr., water q.s. 10 oz.

PHARMACOLOGY

Externally.—Both boric acid and borax are non-irritating and mild antiseptics. In $2\frac{1}{2}$ p.c. solution almost all forms of bacilli stop growing, but they are not destroyed, *i.e.* they are **bacteriostatic.** Boric acid is also a **fungicide.** They are non-toxic to the tissues and do not penetrate and are suitable for delicate mucous membrane.

Internally. **Gastro-intestinal tract.**—Taken by the mouth in large doses they cause gastro-intestinal irritation, evidenced by vomiting and purging. Both borax and boric acid are rapidly absorbed by the bowel, and do not affect the intestinal putrefaction.

Urinary tract.—Boric acid and borax are rapidly excreted in the urine, causing increase in the elimination of both water and urea. But the elimination becomes slow after twelve hours so that boric acid may be cumulative. Borax, like any other alkaline preparation, renders the urine alkaline. They are genito-urinary antiseptics, but rarely used now.

Toxic action.—Boric acid was used as a food preservative, but owing to cases of poisoning its use has been prohibited. The symptoms are loss of appetite, mild gastro-enteritis, muscular weakness, albuminuria and prostration. The prolonged use, either internally or externally, has led to falling of the hair, eczema and psoriasis. Oedema and swelling of the skin may appear, and a gray line on the gums, similar to that seen in lead poisoning, is stated to occur along with irritation of the mouth. Also bullous, cutaneous lesions or a dermatitis. Renal disease seems to increase the susceptibility to poisoning.

THERAPEUTICS

Externally.—Being non-irritant, boric acid is largely used in surgical dressings. As an antiseptic dusting

powder it is used mixed with starch (1 in 4) or zinc oxide and talc. The ointment is applied to wounds, ulcers and burns. As its action is entirely local its use is of no value in deep suppurating cavities. It is used as an eye-wash in ophthalmia (15 gr. in 1 oz. of distilled water) either alone or with alum or sulphate of zinc ; and as an injection in leucorrhoea, gonorrhoea, ozaena (10 grs. to 1 oz.) and otorrhoea. In cystitis, the irrigation of boric acid (1 in 100) is a useful local application. Pityriasis of the body and scalp, eczema of the ear and scalp, and cracked nipples are benefited by boric acid applications. Borax (60 grs. to water 4 ozs.) removes prurigo of the labia and anus.

Internally.—Borax is used as a gargle in mercurial salivation and aphthous sores of the mouth. Borax tablets slowly dissolved in the mouth reduce hoarseness. Tincture of myrrh and borax is a valuable local paint for ulcerated gums, and makes a good mouth-wash. Glycer. boracis is a soothing and antiseptic application to inflamed mucous membrane and is specially useful in thrush.

Prescribing hints.—Borax being alkaline should not be combined with cocaine or other alkaloids. Combined with acetate of lead or sulphate of zinc insoluble borates are precipitated. Being alkaline it liberates chloroform when prescribed with chloral hydrate.

SODII METABISULPHIS. (Sod. Metabisulphis). **Syn.**—Sodium Bisulphis.—Sodium Metabisulphite may be prepared by saturating a solution of sodium hydroxide with sulphur dioxide and allowing to crystallise.

Characters.—Colourless prismatic crystals or a white powder, becoming yellowish on keeping ; odour, sulphurous ; taste, acid and saline. *Soluble* in about 2 parts of water ; less soluble in alcohol (95 p.c.).
Enters into.—Inj. Adrenal., Inj. Apomorph. Hydrochlor., Inj. Physostig. Salicyl., Inj. Procain. et Adrenal. Fort., Inj. Stibophen., Liq. Adrenal. Hydrochlor.

ACTION AND USES.—It is an antiseptic and antifermentative and is used as a food preservative and to prevent decomposition of Inj. Procainae et Adrenalin. and other injections. A 10 p.c. lotion is useful in ringworm and other skin diseases. As a throat paint it is used combined with Glycerin and Ol. Menth. Pip.

II. Parasiticides

Parasiticides are divided according to their action on the different varieties of parasites as follows :—

1. Tinea and its varieties : **Mercury** (*see* p. 502), **Iodine** (*see* p. 710), **Phenol** (*see* p. 714), **Salicylic Acid** (*see* p. 462), **Boric Acid** (*see* p. 726), **Thymol** (*see* p. 701), **Formalin** (*see* p. 726), **Chrysarobin, Dithranol.**

2. Scabies or itch : **Sulphur, Benzyl Benzoate, Ichthammol, Mesulphen, Storax** (*see* p. 685), **Balsam of Peru** (*see* p. 685), **Sandal Wood Oil** (*see* p. 420).

3. Pediculi or lice : **Dicophane, Lauryl Thiocyanate, Lethane 384 Special, Derris, Benzyl Benzoate** (*see* p. 732), **Mercury** (*see* p. 502).

1. Drugs used in Tinea and its Varieties

CHRYSAROBINUM, B. P. C. (Chrysarob.). Chrysarobin.

Source.—A mixture of substances obtained from araroba, by extracting with hot benzene, evaporating to dryness and powdering.
Characters.—A light, microcrystalline, yellow, tasteless, inodorous powder. *Solubility.*—Entirely in hot chloroform and in hot benzene, slightly in alcohol (90 p.c.), almost insoluble in water.
Composition.—(1) *Chrysophanolanthranol.* (2) *Chrysophanic Acid.*

Non-official Preparations

1. **Unguentum Chrysarobini, B. P. C.**—Chrysarobin 4, Simple Ointment 96.
2. **Unguentum Acidi Chrysophanici** (Malcolm Morris).—Acid Chrysophanic 20 grs., Paraffin Liquid 2 drs., Lanolin to 1 oz.

Action and Uses

Chrysarobin is a powerful irritant to the skin but does not irritate so much the diseased parts as the healthy skin. It is a valuable remedy for **ringworm** and other forms of skin diseases, such as psoriasis, eczema, and acne rosacea. It is generally used in the form of ointment but it has the disadvantage of staining the skin and clothing. For this reason many prefer to use it mixed with collodion (Chrysarobin 4 grms. dissolved in 30 mils of Collod. Flex.). This is painted with a camel hair brush. After it dries up it may be coated with plain collodion for further protection against staining.

DITHRANOL. $C_{14}H_{10}O_3$. **Syn.**—Dioxyanthranol; Anthralin; Cignolin.—It is 1 : 8-dihydroxyanthranol. In odourless, yellow powder. *Insoluble* in water, slightly soluble in alcohol (95 p.c.), and in solvent ether; soluble in chloroform, in acetone and in fixed oils.

Official Preparation

1. **Unguentum Dithranolis.**—0.1 p. c.

Uses.—It is a chemical relative of the most important constituent of chrysarobin and used in the treatment of psoriasis and is three or four times stronger than chrysarobin, but less irritant to the skin and kidneys, does not cause dermatitis and less liable to cause staining of the linen. It is generally used either as an ointment (0.25 to 1 p.c.) or in solution as a paint. It may also be used in chronic eczema, alopecia areata, and fungus infections of the skin. For application to the head or face a 0.1 p.c. ointment should be first used to test the sensitiveness of the patient to excessive reaction of the drug.

2. Drugs used in Scabies

SULPHUR SUBLIMATUM

(Sulphur. Sublim.)

Syn.—Flowers of Sulphur.

Source.—Sublimed Sulphur is obtained from native sulphur, or from sulphides.

Characters.—A fine, yellow, slightly gritty powder; odour, faint not unpleasant; tasteless. Burns with a blue flame forming sulphur dioxide. *Almost insoluble* in water, in alcohol (90 p.c.), incompletely soluble in carbon disulphide.

B. P. Dose.—15 to 60 grs. or 1 to 4 grms.
Enters into.—Pulv. glycyrrhizae co.

Official Preparation

1. **Unguentum Sulphuris.**—Sublimed sulphur, 10 p.c.

Non-official Preparations

1. **Confectio Guaiaci Co., B. P. C.** *Syn.*—*Chelsea Pensioner.*—Guaiacum resin 10, rhubarb 20, acid potassium tartrate 75, nutmeg 10, sublimed sulphur 145, honey 740. *Dose.*—**60 to 120 gr. or 4 to 8 grm.**
2. **Unguentum Acidi Salicylici et Sulphuris, B. P. C.**—Salicylic acid and sublimed sulphur each 3 grm., hydrous ointment 940 grm.

SULPHUR PRAECIPITATUM. (Sulphur. Praecip.). **Syn.**—Milk of Sulphur.

Source.—Precipitated Sulphur is obtained by adding hydrochloric acid to a solution prepared by boiling sulphur and lime with water.

Characters.—A pale greyish-yellow or pale greenish-yellow, soft powder, free from grittiness; tasteless, and free from odour of hydrogen sulphide. Burns with a blue flame forming sulphur dioxide. *Almost insoluble* in water, in alcohol (90 p.c.), almost completely soluble in carbon disulphide.

B. P. Dose.—15 to 60 grs. or 1 to 4 grms.

PHARMACOLOGY

Externally.—When applied to the skin pure sulphur has no effect, but if it be mixed with any greasy substance (sebaceous secretion), some of it is converted into sulphide which acts as a mild irritant and **parasiticide** and causes death of the itch insect. When it is brought into contact with open wound, more sulphide is formed which causes more severe irritation to raw surfaces, and sometimes destruction of tissues.

Internally. **Gastro-intestinal tract.**—Being insoluble in the fluids of the mouth, sulphur has no taste, neither does it undergo any change in the stomach. In the intestine it is converted into alkaline sulphide and sulphuretted hydrogen which stimulate the peristalsis and act as **laxative** in ten to twelve hours. The stools are soft and owing to the presence of sulphuretted hydrogen gas, the smell is offensive.

Clearance.—Sulphur is excreted mostly unchanged by the stool, rest as sulphates by the urine, about 10 to 40 p. c. is absorbed as sulphide and excreted by the lungs, sweat and milk. It gives an offensive smell to the breath, and blackens silver ornaments worn next the skin.

THERAPEUTICS

Externally.—Sulphur is largely used to disinfect infected rooms. For this purpose about a pound of sulphur is broken and moistened with methylated spirit and allowed to burn in a vessel. The active agent is SO_2 gas, which by acting as a reducing agent, acts as a powerful disinfectant. About two pounds when burnt will give off over 2 p. c. of gas to the atmosphere of the room and will disinfect a room of 1000 cubic feet.

It is chiefly used in the treatment of **scabies** and **itch.*** If thoroughly applied it is certain in its effects and provided the strength is properly adjusted to the condition of the patient's skin no undue irritation is caused. The gritty sublimed sulphur is better as it mechanically opens up the burrows and brings the drug into closer contact with the acarus, the eggs and embryos of which lie beneath the

*Acid. salicyl.	gr. 15
Ung. sulph.	dr. 4
Ung. hydrarg. ammon.	dr. 2
Ung. simp.	dr. 2

superficial layers of the epidermis. On account of the irritation and disagreeable smell some use Storax or Balsam of Peru.

If scabies be complicated by eczema and impetigo, the best preparation to use is Ung. Acid. Salicylic. et Sulphuris B.P.C. This ointment accompanied by the use of warm bath, is applied twice daily, and cures in three days.

For the cure of **acne** the following lotion* is better than the ointment which is a very unsightly application to the face.

Internally.—Sulphur is largely used as a laxative, and as it causes soft motions without any pain it is specially used in haemorrhoids and fissures of the anus. Too long use leads to dyspepsia and catarrh of the bowels. It is given in plumbism to prevent reabsorption of lead from the intestines. In the form of *Chelsea Pensioner* it is a favourite remedy in chronic rheumatism and gout. Sulphur (0.1 to 2 p.c.) dissolved in olive oil, or colloidal sulphur given intramuscularly, has been recommended in arthritis deformans and chronic rheumatic polyarthritis.

POTASSA SULPHURATA, B. P. C. (Potass. Sulphur.). **Syn.**—Liver of Sulphur.—Sulphurated Potash is a mixture of salts of potassium, chiefly sulphides.

Characters.—Solid fragments, externally greenish-yellow, internally pale liver-brown, rapidly changing to greenish-yellow on exposure to air ; odour of hydrogen sulphide. Taste, alkaline, acrid. *Soluble* in water.

Calx Sulphurata, B. P. C. **Syn.**—Calcium Sulphide.—A greyish-white powder with a smell of hydrogen sulphide.

Dose.—1/4 to 1 gr. or 16 to 60 mg.

Non-official Preparation

1. **Liquor Calcis Sulphuratae, B. P. C.** *Syn.—Lotio Calcis Sulphuratae ; Vleminckx's Solution.*—Calcium hydroxide 25 grm., sublimed sulphur 50 grm., water q.s. 1000 mil. Boil till sulphur is dissolved.

Pharmacology

Externally.—Both sulphurated lime and sulphurated potash are irritants and parasiticides. Sulphides, specially of calcium and barium, are depilatories.

Internally.—Sulphides are decomposed in the stomach into sulphuretted hydrogen to which they owe their virtues. In the stomach they act as local irritants, and in the intestine stimulate peristalsis and act as purgatives. The gas however gives rise to disagreeable eructations.

Therapeutics

Externally.—Sulphurated potash in the form of an ointment† may be used in place of sulphur ointment in the treatment of scabies, but a better preparation is Lotio Calcis Sulphuratae or Vleminckx's Solution.

*Sulph. praecip.	gr. 60
Glycer.	oz. 1
Aq. rosae	oz. 10

†Potass. sulphur.	grs. 60
Sod. carb.	grs. 60
Ung. simp.	oz. 1

In the form of a bath (4 ozs. to 30 gals. of water) sulphurated potash is used in chronic rheumatic arthritis and myalgia, chronic nervous diseases, and in chronic metallic poisoning. Sulphide baths with the internal administration of mercury constitute the celebrated Aix treatment, for syphilis.

Internally.—Calcium sulphide is used as a remedy for furunculosis and acne.

ICHTHAMMOL. (Ichtham.). **Syn.**—Ammonium Ichthosulphonate ; Ichthyol.

Source.—Ichthammol consists of the ammonium salts of the sulphonic acids of an oily substance, prepared from a bituminous schist, together with ammonium sulphate and water. Contains not less than 10.5 p.c. w/w of organically combined sulphur.

Characters.—An almost black, viscid liquid. *Soluble* in water, partly in alcohol (90 p. c.), miscible with glycerin and with fixed oils.

Pharmacology and Therapeutics

Ichthammol contains a high percentage of sulphur, and possesses mild irritant, antiseptic and antiparasitic properties. As an antiseptic it is less powerful than phenol. It is a mild astringent to mucous surface and exposed tissue. An ointment (5 p.c. with lanolin), alone or combined with zinc oxide, forms an excellent application in obstinate cases of ulcerative blepharitis. It forms a valuable application in mumps. It has been used in a large variety of skin diseases, specially acne and furunculosis and is a mild counter-irritant in rheumatic conditions and sprained joints. To aid absorption of inflammatory products it is used in gynaecological practice as tampons with glycerin (5, 10 or 20 p.c.).

BENZYLIS BENZOAS. (Benzyl. Benz.). **Syn.**—Spasmodin.

Source and Characters.—Benzyl Benzoate is prepared by the esterification of benzyl alcohol with benzoic acid. Colourless crystals or a colourless oily liquid ; odour faintly aromatic ; taste, sharp and burning. *Insoluble* in water, soluble in alcohol (90 p.c.), in chloroform and in solvent ether, insoluble in glycerin.

Non-official Preparation

1. **Applicatio Benzylis Benzoatis, B. P. C.**—Benzyl benzoate 25 grm., emulsifying wax 2 grm., water q.s. 100 mil.

Action and Uses.—On the idea that the benzyl radical of papaverine was responsible for the depressant effects on the involuntary muscle, benzyl benzoate was introduced by Macht to relax smooth muscle. It was therefore used in the treatment of various spasmodic conditions, *e.g.* intestinal, biliary and renal colics, dysmenorrhoea, bronchial asthma, etc., but the results were not uniform and failed to give relief except in spasm of the stomach and intestine. Given in large doses it irritates the alimentary canal causing vomiting and diarrhoea. The usual mode of administration is as an alcoholic solution (1 in 5), and then

diluted with water, when it forms a milky solution, or as an emulsion in doses of 5 to 8 ms.

It has been used with success in the treatment of **scabies.** It is applied mixed with equal parts of soft soap and rectified spirit, or equal parts benzyl benzoate (25 p.c.) and emulsifying wax (2 p.c.) in water, or as emulsion. The method of application is as follows : The patient anoints the whole body with soft soap, specially the affected parts. He then rubs himself for 10 minutes in a bath of 100°F. and after drying applies the lotion for 10 minutes over the whole body from the neck downwards. After drying, a further application is made for 5 minutes and after gently drying with towel puts on his clothes. After 24 hours a second bath is taken and clean clothes are put on, the dirty ones being allowed to sterilize. The same emulsion has been used with good results in **pediculosis capitis.**

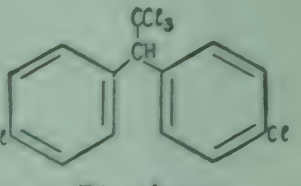
Mesulphenum, B. P. C. Syn.—Mitigal.—It consists of 2 : 6-dimethylthianthrene. Occurs as yellow somewhat viscid, oily liquid, with a slight but not unpleasant odour. Contains 25 p.c. sulphur in organic combination.

Uses.—It is used in the treatment of various parasitic skin diseases, *e. g.* scabies, pediculosis, impetigo, etc. It is specially valuable for application to the hairy parts. The part should be properly cleaned and applied for successive days.

3. Drugs used in Pediculosis

DICOPHANUM. Syn.—DDT.—Dicophane consists chiefly of 1 : 1 : 1-trichloro-2 : 2-di-(*p*-chlorophenyl) ethane. White or nearly white crystals, powder or small granules ; odourless or with a slight aromatic odour. Almost insoluble in water ; readily soluble in benzene and in carbon tetrachloride ; soluble in about 50 parts of alcohol (95 p.c.).

Characters.—Insoluble in water and benzene, slightly soluble in cold alcohol and acetic acid. Readily soluble in hot alcohol, chloroform, ether and freely in carbon tetrachloride.



Dicophane

Lauryl Thiocyanate (Technical). (Not official). **Syn.**—Lauryl Rhodanate.—Contains lauryl thiocyanate 60 p.c. and certain homologues 40 p.c.

Lethane 384 Special. (Not Official).—Contains N-butyl carbitol thiocyanate 12.5 p.c. ; beta-thiocyanoethyllaurate 37.5 p.c. ; refined paraffin 50 p.c.

Derris, I.P.L. **Syn.**—Indian Tuba Root.—Consists of dry rhizome and root of *Derris ferruginea*, collected from two years old plants. Contains not less than 2 p.c. *Rotenone.*

Non-official Preparations

1. **Derris Cream.**—A solution of derris extract in castor oil, emulsified with stearic wax to form a suitable cream. Contains 1 p. c. rotenone and 7 p. c. derris extract.
2. **Applicatio Derridis, I.P.L.**—Derris 1, hard soap 0.25, water 10.

Uses.—All these are valuable **insecticides.** Of these dicophane either applied in the form of oil solution or as a watery emulsion has remarkable residual effect, killing all mosquitoes and flies which

rest on the sprayed surface for many days. It is also a valuable **larvicide**. Dicophane has been used with success in the control of mosquitoes as a preventive against malaria. Similarly epidemics of typhus has been checked by eliminating body lice from infested people. For this purpose it is mixed with purified talc powder (2 to 10 p.c.) and blown between the skin and clothing of infested people.

All these are used in the treatment of **pediculosis**. Dicophane emulsion (2 p.c.) not only kills the lice but persists in the hair long enough to kill all the larvae. The action of lethane does not persist long and some larvae which hatch towards the end of the first week after treatment may survive. The smell of D. D. T. emulsion is not unpleasant and the hair looks natural after treatment, and being insoluble in water, the hair can be washed. Anti-louse powder containing 5 p.c. dicophane is quite efficacious. Any of the above may be applied as follows :—

Two to three teaspoonfuls are used for one application. The hair should be parted and the emulsion or cream put on the scalp with the spoon or pipette, 2 to 3 drops at a place, and repeated in from 20 to 30 different areas all over the scalp ; the material is then distributed by vigorously rubbing with the fingers ; comb should not be used and the head should not be washed for ten days.

Derris root, either as lotion, cream or as rotenone ointment (1 to 2 p. c.) will cure scabies in three or four days when applied after a bath with soft soap.

III. Insecticides

Gammexane, Dicophane, Derris

Gammexane. (Not official).—Gammexane is prepared by the interaction of chlorine and benzene, the product benzene hexachloride (BHC) consists of four isomers, *alpha*, *beta*, *gamma* and *delta*. Since the gamma isomer has been found to be entirely responsible for the insecticide property, it is separated from the other isomers and is present in gammexane to the extent of 13 p.c. and is known as gamma BHC.

It is a white solid insoluble in water, but soluble in alcohol, acetone, benzene, chloroform and naphtha.

USES.—Gammexane is effective against almost the same insects as dicophane, namely, flies, mosquitoes, lice, bed-bugs, fleas, cockroaches, etc., but it kills in lower concentration and more quickly. It may be used in the form of "dust," "sprays," or as "smoke."

Usual diluent for use as "dust" is road dust, chalk, talc or powdered soapstone. It can be applied by hand with a rotary duster. This may be applied over compost heaps, refuse dump, manure heaps, night-soil trenches and other places where flies generally breed. One application will prevent breeding for about five weeks. Similarly it may be applied over other places where bed-bugs and fleas are generally found. For control of adult mosquitoes or larva (both anophelene and culex) it may be used as spray diluted with kerosene, or as dust. As a smoke it is used in the form of special smoke generator, and is valuable for disinfestation of houses, godowns, ships, public transports, etc. It is particularly valuable for controlling insect pests of godowns where food grains are stored.

GROUP XXV

DRUGS ACTING ON THE SKIN

The skin is one of the most important organs of the human body performing diverse functions. It protects the underlying structures, regulates the body temperature by

variations in the blood supply and sweat formation, and plays an important part in the general metabolism by absorbing the ultra-violet rays and utilising them in the formation of vitamin D so important for growth and nutrition. Being highly differentiated tissue and being freely supplied with sensory nerves, it reflexly affects respiration and circulation, and any injury to the skin is followed by local and general effects depending upon the nature and intensity of the damage. Thus the symptoms of poisoning and shock which follow extensive injury to the skin, as happens after burns, are attributed to the absorption of the break-down products of histamine-like substances. Skin rash is a common accompaniment of many poisons and infections, and it is possible that it plays an important part in the defensive reactions that protect the body from microbic invasion.

Sweat.—Secretion of sweat is an important function of the skin and is performed by the sweat glands. Although an excretion, inasmuch as it helps elimination of water, salts and nitrogenous end products, it regulates the body temperature by the evaporation of the water. The total amount of water lost in 24 hours is about 500 to 700 mils and may be greater under special circumstances. The reaction of human sweat is acid, due to the presence of fatty acids, derived from the sebaceous glands. The secretion of sweat differs from the urine in that it is influenced by nerves and is independent of blood pressure or general circulation ; in fact there is abundant sweat when the skin circulation is almost nil, as for instance, the cold sweat and death sweat ; although increase of blood volume, as happens after drinking large quantities of water, is followed by diaphoresis.

The sweat glands are supplied by the sympathetic and are also under the control of the central nervous system. Pharmacologically the peripheral mechanism of the sweat glands acts as if they are innervated by the parasympathetic, *i.e.* the nerves are cholinergic. Adrenaline, which stimulates the sympathetic, produces no effect on sweat secretion. Meyer and Gottlieb hold that the sweat glands receive in general augmentor nerves from both the autonomic system, and that in man and certain animals only the parasympathetic endings are accessible to the action of drugs.

Drugs that increase the secretion of sweat are called **diaphoretics or sudorifics.** They act as follows :—

1. *By directly stimulating the centre.*—Drugs which stimulate the spinal centres also stimulate the spinal sweat centres. The following drugs stimulate the centre and cause diaphoresis ; they are ammonium acetate, ammonium citrate, and camphor. The centre is also stimulated by venous blood.

2. *By stimulating the nerve-endings.*—Pilocarpine is most

powerful in this respect. Physostigmine, acetylcholine and muscarine act similarly.

3. *By dilating the cutaneous vessels.*—As by local heat, hot baths, turkish baths, hot drinks, or by drugs which specifically dilate vessels of the skin, as alcohol, opium (Dover's powder), chloral hydrate, salicylates, antipyretics, etc.

4. *Reflex stimulation of the centre.*—The use of emetics, such as antimony and ipecacuanha, will produce perspiration through reflex stimulation. Other examples of this are sweating in nausea and during psychical stimulation of the cerebrum, as from fear or anxiety.

Therapeutics.—Diaphoretics are indicated :—

(*a*) To reduce pyrexia.

(*b*) To cut short a threatening catarrh or inflammation caused by specific poisons or metabolic products.

(*c*) To lessen the accumulation of fluid in the system, as in dropsy, and to relieve excretory organs, *e.g.* kidneys in albuminuria.

(*d*) To eliminate excrementitious products through the skin when the action of the kidneys is suspended, as in uraemia. Pilocarpine is most useful for this purpose.

Drugs which diminish the sweat are known as **anhidrotics.** They may act as follows :—

1. *By depressing the ends of the secretory nerves.*—The effect of atropine is most powerful.

2. *By lessening the activity of the sensory nerves*, as by cold application, cool atmosphere, etc.

Drugs that affect the hair.—The hairs are epidermal growths contained in pits or hair-follicles. Except certain parts, the whole body surface is covered with hair. But the growth of hair on the scalp, face, axillae and in the regions of the external genitals are controlled in a varying degree by the sex hormones. The pituitary and thyroid glands also influence the growth of hair. The influence of nerves on the growth of hair has not been satisfactorily established.

When baldness is due to defective nutrition as happens after prolonged illness, general tonics and stimulating applications like cantharidin, rosemary, capsicum, quinine and pilocarpine in the form of lotions are useful. When due to metabolic disturbance, the use of drugs to supply the deficient internal secretion like thyroid or pituitary is indicated.

Depilatories are drugs used to remove hairs. These may be (*a*) *local*, and the effects depend upon the presence of a sulphide and an alkali. The freshly prepared paste is applied in a thick layer over the part and allowed to remain for 5 to 10 minutes and then scraped off with a blunt knife, and cold cream applied to the inflamed skin. Barium sulphide (*see* page 108) is largely used for the purpose. It dissolves the hair shafts and causes them to break off leaving the skin quite clean and bald ; (*b*) *internal*, *e.g.* thallium (*see* page 131).

CLASS A : Irritants and Counter Irritants

These are drugs or measures which relieve inflammation or congestion of some internal organs by producing local irritation. The use of irritants for various purposes is one of remote antiquity, but the method of doing this has not always been the same, yet burning with hot iron, cautery, application of blisters and the use of irritant plants to produce local irritation or inflammation are still

to be found. The principle however remains, and instead of the violent methods milder remedies are now used.

All these drugs act by stimulating the nerve-endings which produce (1) local vaso-dilatation and inflammation due to axon reflexes ; (2) vaso-dilatation of distant organs due to axon reflexes acting through the posterior root ; and (3) medullary reflexes affecting respiration and circulation (Clark).

The effects of counter-irritation are local, general and remote. The local effects may be mild being limited to production of congestion and redness of the skin, *i.e.* rubefaction, and the drugs producing these effects are known as **rubefacients.** In this stage there is arterial and capillary congestion, at first active, later passive, and is usually accompanied by sensory stimulation with itching, burning and pain. These effects are axon reflexes, *i.e.* the vaso-dilatation with all its accompaniments occurs without the impulses passing through a nerve cell. The condition of the skin returns to normal without leaving any local lesion. If the irritation is too strong, or if the irritant is allowed to remain for a longer period, little vesicles appear, which eventually coalesce and form one large blister, and the drug producing this effect is known as **vesicant.** In both these conditions exudation occurs, but when the exudate is greater than can be removed by the lymphatics, it collects forming a blister. If the application is mild, or not continued long, the effects following application of rubefacients or vesicants resemble those of local inflammation. If the irritation is very severe and the irritant does not penetrate the epidermis but only the cutaneous glands, pustules form, which are at first discrete but later become confluent, and drugs which produce these effects are known as **pustulants,** *e.g.* tartar emetic and croton oil. **Caustics or escharotics** destroy the vitality of the part on which they are applied. They cause sloughing and inflammation of the surrounding area, *e.g.* zinc chloride, potassium or sodium hydroxide.

Apart from local effects the drugs of this group produce certain general changes, due to reflex stimulation of the vital medullary centres, *viz.*, the cardiac, vaso-motor and respiratory. The results are not uniform and depend upon the intensity of the irritation produced. A mild irritation accelerates the heart and raises the blood pressure : while a more powerful irritation slows the heart through vagus stimulation with fall of pressure due to enormous dilatation of the splanchnic vessels. Similarly respiration is stimulated by mild irritation, *e.g.* sinapism, or application of cold douche on the face in narcotic poisoning, faintness, or hysteria. Owing to the changes in the distribution of the blood through vaso-motor disturbance,

the temperature varies. There is leucocytosis specially after the use of vesicants, while the absorption of oxygen and elimination of carbon dioxide are augmented.

The exact manner in which the counter-irritants act and exert their beneficial effects on distant organs is still a matter of dispute. Much light has however been thrown by the work of Head and Mackenzie, who have shown a relationship between the viscera and certain skin areas and body wall through the nervous system. They pointed out that the tenderness of the superficial tissues may be a manifestation of inflammation or injury of one of the internal organs. Thus tenderness of the skin and muscle of the epigastrium implies ulcer of the stomach. In many instances the pain is referred to situations remote from the organs giving rise to it. Thus the pain of biliary colic may be felt in the epigastrium, that of renal colic in the testicle, that of heart affections in the left arm. These tender areas or Head's areas do not correspond to posterior nerve roots but to their segmental relations. According to Head the spinal cord and brain are regular segments and that a lesion implicating a nerve from a particular segment affects all the nerves whose centres are in that segment. It is possible that the good effects which follow application of counter-irritants may be the result of conferred hypersensitiveness to stimuli, to reflex changes in the circulation, or perhaps to psychical effects on the mind.

Therapeutics.—Counter-irritants are indicated as follows :—

(1) To subdue inflammation or to afford relief to the circulation of a part or organ in direct vascular connection with the skin selected for the application of rubefacients or vesicants ; *e.g.* the application of a blister in pleurisy, hepatitis, etc.

(2) To help absorption of subjacent or subcutaneous morbid growths or effusion, *e.g.* the application of flying blisters in pleuritic effusion and synovitis, and of iodine in enlarged glands.

(3) To relieve pain from neuralgia and rheumatic affections.

(4) To allay central nervous irritability, as in hysteria.

(5) To reflexly stimulate the central nervous system ; as in syncope, narcotic poisoning.

Counter-irritants are :—**Cantharidin, Capsicum, Iodine, Mustard, and Volatile Oils.**

CANTHARIDINUM, B. P. C. (Cantharidin.). $C_{10}H_{12}O_4$.

Source.—Cantharidin is obtained from various species of *Cantharis* (Spanish fly), or of *Mylabris.*

Characters.—White glistening crystals ; inodorous. Very sparingly soluble in water, soluble in about 1100 parts of alcohol (90 p. c.). More soluble in chloroform, acetone and fixed oils.

Non-official Preparations

1. **Emplastrum Cantharidini in Massa, B. P. C.** *Syn.—Blistering Plaster-mass.*—0.2 p.c. cantharidin.
2. **Liquor Epispasticus, B. P. C.** *Syn.—Blistering Liquid.*—0.4 p.c. cantharidin.

Pharmacology

Externally.—Locally cantharidin is an **irritant, rubefacient** and **vesicant** but its action is slow and does not show any sign until after

two or three hours, when tingling and burning are felt followed by redness and subsequently form vesicles.

Internally.—The same irritant effect is observed in the mouth, fauces, stomach and intestine, producing burning pain in the mouth, throat, and abdomen with vomiting and purging. Both the vomit and the stool may contain blood. Whether absorbed from the skin or stomach it is slowly excreted by the kidneys and irritate the bladder with frequent desire to micturate. Large doses produce pain in the loins, albuminuria, haematuria and inflammation of the bladder producing intense pain and priapism in men and abortion in women.

THERAPEUTICS

It is rarely used internally and its use as a counter-irritant is also becoming rare. It is however used to stimulate growth of hair as an ingredient for hair oils or hair lotions. (See page 688.)

CLASS B : Emollients and Demulcents

Emollients are drugs which soften or relax the skin upon which they are applied. They are bland, oily or fatty substances and prevent cracking of the skin by supplying it with fat or moisture. *Demulcents* are substances of a viscid character which protect mucous membranes from irritation.

Emollients and demulcents are :—

Olive Oil, Sesame Oil, Cottonseed Oil, Almond Oil, Linseed Oil, Archis Oil, Glycerin, Honey, Liquorice, Acacia, Tragacanth, Starch.

OLEUM OLIVAE

(Ol. Oliv.)

Source.—Olive oil is a fixed oil expressed from the ripe fruit of ***Olea europaea.***

Characters.—Pale yellow, or greenish-yellow, liquid with faint odour and bland taste. Slightly *soluble* in alcohol (90 p. c.), miscible with solvent ether, with chloroform, and with light petroleum.

Composition.—(1) *Olein*, glyceride of oleic acid, 93 p. c. ; and (2) *Linolein*, glyceride of linoleic acid, 7 p.c. (3) *Palmitin*, a solid oil composed of palmitic acid and glyceryl. (4) *Arachin.*

B. P. Dose.—1/2 to 1 oz. or 15 to 30 mils.

Enters into.—Ung. Hydrarg. Co. and Ung. Hydrarg. Nit. Fort.

PHARMACOLOGY AND THERAPEUTICS

Externally.—Olive oil being a bland unirritating fixed oil is usually applied as an emollient in dry skin diseases, such as psoriasis and xeroderma. It forms a basis for liniments and ointments, and as a lubricating agent is employed in massage. It softens and aids the removal of the scabs of eczema, favus, etc. Mixed with 4 or 5 p.c. of phenol, it is applied in the desquamative stage of scarlatina and small-pox. Lin. calcis (lime water 1, olive oil 2) is a soothing protective to burns and scalds. The oil is absorbed by the cutaneous lymphatics, and gives nutrition to the tissues, but not to the same extent as is done by cod-liver oil.

Internally.—As a demulcent, it is useful in irritant poisoning, except by phosphorus. In large doses (1 to 2 ozs.) it lubricates the gut and is a mild laxative, producing painless, soft stools, and is therefore of value

in inflamed and ulcerated piles, rectal ulcers, anal fissures, and constipation. It acts also as a laxative when given as an **enema** (4 ozs. to ½ pint of starch mucilage), and in faecal impaction (5 to 20 ozs.). It is also used as a vehicle for rectal administration of ether and paraldehyde and for the hypodermic use of ether and camphor.

Because the cholesterine of the gall-stone is soluble in pure olive oil at the normal bodily temperature, it has been recommended as a solvent for gall-stones on the supposition that some of the constituents of the oil are excreted with the bile, but as there is not the slightest evidence that the oil can reach the gall-stone in the gall-bladder or cystic duct, its value is doubtful. It reduces the acid secretion of the stomach, and by stimulating contraction of the gall-bladder helps excretion of bile. Its use has therefore been advocated in gastric ulcer and in dyspepsia without ulcer, but where the symptoms are similar to those of ulcer. In various disorders of the gall-bladder, such as cholecystitis without stones, cholelithiasis and in atony of the gall-bladder its use relieves the symptoms. It may be administered alone in capsules or in the form of emulsion.

OLEUM SESAMI. (Ol. Sesam.). **Syn.**—Teel Oil; Gingelli Oil.

Source.—Sesame Oil is the fixed oil expressed from the seeds of *Sesamum indicum.*

Characters.—A pale yellow liquid; faint odour; bland taste. Slightly *soluble* in alcohol (90 p.c.), miscible with solvent ether, with chloroform and with light petroleum.

Composition.—(1) *Sesamin*, a crystalline substance and *Sesamolin.* (2) Liquid fats, 70 p.c. consisting of *glycerides of oleic and linoleic acids.* (3) Sesamol, a phenol. (4) *Solid fats*, 12 to 14 p.c. stearin, palmitin, etc.

Uses.—Sesame oil possesses unusual property of stability possibly because of sesamin and sesamolin. It is used as a vehicle for medicaments to be administered subcutaneously or intramuscularly, chiefly for oestrogenic substances. Used as a *substitute for olive oil* to make liniments, ointments and plasters.

OLEUM GOSSYPII SEMINIS. (Ol. Gossyp. Sem.).

Source.—Cottonseed Oil is a fixed oil obtained from the seeds of various cultivated species of *Gossypium.*

Characters.—Pale yellow, or yellow, oil. Almost odourless, with a bland taste. Slightly *soluble* in alcohol (90 p.c.), miscible with solvent ether and chloroform and with light petroleum. If it solidifies it should be gently warmed and thoroughly mixed before use.

Composition.—Glycerides of oleic, linoleic, stearic and palmitic acids.

Uses.—It is used for the same purposes as olive oil. Being cheap it is preferred to other oils for external use.

OLEUM AMYGDALAE. (Ol. Amygdal.). **Syn.**—Oleum Amygdalae Expressum, U.S.P.—Almond Oil is the fixed oil obtained from the seeds of *Prunus amygdalus* var. *dulcis*, or of *P. amygdalus* var. *amara.*

Characters.—Pale yellow, nearly inodorous, with a bland. nutty taste. *Solubility.*—Miscible with solvent ether, with chloroform, slightly soluble in alcohol (90 p.c.).

Composition.—Chiefly olein and linolein.

B. P. Dose.—1/2 to 1 oz. or 15 to 30 mils.

Oleum Amygdalae Volatile Purificatum. (Ol. Amygdal. Vol. Purif.).—Purified Volatile Oil of Bitter Almond is prepared from the cake left after pressing out the fixed oil from bitter almonds, peach kernels, or apricot kernels, by distillation with water, and freed from hydrocyanic acid.

Characters.—A colourless or pale yellow liquid ; odour and taste, that of bitter almonds. Soluble in 2 parts of alcohol (70 p.c.). Should be kept in well-closed containers, protected from light, and stored in a cool place.
Enters into.—Emulsio Olei Morrhuae.

Pharmacology and Therapeutics

Externally.—Almond oil is a demulcent and emollient, and being a bland oil makes a good basis for many hair-oils and ointments. It is a soothing application for chapped hands, excoriations and irritable skin diseases.

Internally.—Sweet almond is nutritive. Its flour being devoid of starch is given to diabetic patients as a substitute for starchy food.

The oil is a mild purgative in 120 to 240 ms. doses. An enema of 1 to 3 pints of the oil is effective in impaction of faeces. It is pleasanter than olive oil, but expense limits its use and leads to frequent adulteration.

Purified volatile oil of bitter almond is used as a flavouring agent for cod-liver oil emulsion.

OLEUM LINI. (Ol. Lini).—Linseed Oil is the fixed oil expressed from the ripe seeds of *Linum usitatissimum.*

Characters.—A yellowish-brown oil ; odour, characteristic ; taste, bland. Gradually thickens when exposed to air, forming, when spread in thin films, a hard transparent varnish. Slightly *soluble* in alcohol (90 p.c.) ; miscible with solvent ether, with chloroform, and with light petroleum.
Enters into.—Liquor Cresolis Saponatus.

Linum Contusum. (Linum Contus.). **B. P. C. Syn.**—Linseed Meal ; Lini Semina Contusa.

Source.—Crushed Linseed is linseed reduced to a coarse powder. Should be recently prepared.
Characters.—A brownish-yellow powder, with visible fragments of brown testa. Odour, bland not pungent or rancid, when mixed with warm water.

Pharmacology and Therapeutics

Externally.—Contused linseed in the form of a warm poultice is used to disperse threatening local inflammations. It acts by dilating the local blood-vessels and by relaxing the tissues relieves the tension and pain caused by pressure over the periphery of the sensory nerves. But if the poultice is too hot it increases pain and tension. Hot linseed meal poultice is an excellent, mild, continuous counter-irritant for deep-seated inflammations, such as pneumonia, bronchitis, broncho-pneumonia, pericarditis, peritonitis, pelvic cellulitis, etc. The counter-irritant effect can be greatly increased by dusting powdered mustard over the surface of the poultice, or mixing it (1 in 16) with the meal.

The oil makes a good emollient application to burns and scalds in the form of Carron Oil (*see* page 103). It can also be used as an *enema* (1 lb.) in impacted conditions of the rectum and lower colon.

OLEUM ARACHIS. (Ol. Arach.). **Syn.**—Nut Oil ; Ground-nut Oil ; Pea-nut Oil ; *China-badamer tel,* Beng. *Mungphali tel,* Hind.

Source.—Archis Oil is the fixed oil expressed from the seeds of *Arachis hypogaea.*

Characters.—Pale-yellow oil ; odour, faint, and nut-like ; taste, bland, nutty. Becomes rancid and thick slowly.
Composition.—*Olein,* also contains the glycerides of *hypogaeic, arachidic* and *linolic acids.*

Pharmacology and Therapeutics

Externally.—The oil makes a good substitute for olive and almond oils and may be used in their stead.

Internally.—Arachis oil like sesame oil is largely used as a vehicle for medicaments to be administered in oil solution or suspension and is used in the preparation of Inj. Penicillin. Oleosa. The seeds are very nutritive as they contain 31.0 p.c. of nitrogenous compounds, 37.8 p.c. of starch and sugar, and 11.8 p.c. of fatty matter. They are largely eaten in India and Africa.

GLYCERINUM. (Glycer.). Glycerin. $C_3H_8O_3$.

Source.—Obtained by the hydrolysis of fats and fixed oils.

Characters.—A clear, colourless, syrupy liquid ; odourless ; taste, sweet, followed by a sensation of warmth. Hygroscopic. Miscible with water, and with alcohol (90 p.c.) ; insoluble in solvent ether, in chloroform, and in fixed oils.

Enters into.—The preparation of all glycerins, Cataplasma Kaolini, Gelat. Zinci.

Official Preparation

1. **Suppositoria Glycerini.—70 p.c.**

Pharmacology

Externally.—Glycerin adheres to the surface to which it is applied and absorbs moisture. It keeps the part moist and does not itself evaporate. It readily penetrates the unbroken skin, and carries with it many substances, such as alkaloids, when mixed with it. It is an antiseptic, emollient and demulcent. It renders the skin supple, especially when diluted with water, undiluted glycerin is irritant to the mucous surface and to the skin.

Internally. **Alimentary canal.**—Undiluted glycerin makes the mouth clammy and sticky. It is easily absorbed and oxidised in the body. In large doses it acts as a **laxative.** Injected into the rectum, it moves the bowels by inducing peristalsis from its local irritant effects caused by the absorption of moisture from the mucous surfaces.

Elimination.—Glycerin is excreted from the body as propionic, formic and other acids. The urine of persons taking glycerin gives the copper and fermentation tests for sugar due to the appearance of reducing product which is not sugar.

Pharmaceutical Uses and Therapeutics

Pharmaceutically.—On account of its valuable physical properties, glycerin is specially fitted for pharmaceutical and dispensing uses. It makes an excellent all-round excipient for pills. It is used in the preparation of suppositories, pessaries, pastilles, jellies, glyco-gelatin preparations and ointments ; and as a solvent for many alkaloids, active principles, acids, alkalies, neutral salts, glucosides, iodine, etc. It is a valuable adjunct to lotion for the skin and the hair. As a flavouring agent it is largely employed as a substitute for syrups in mixtures. As a sweetener

and preserver of mixtures it is admirably suited to the Indian climate.

Externally.—As an *emollient*, glycerin diluted with water (1 in 3), or glycerinum c. aqua rosae (glycerin 2, rose water 3), is the best application for chapped lips and hands, rough, dry, furfuraceous skin and for every kind of skin disease, such as herpes, eczema, etc., which require an emollient. Mixed with boric acid it is serviceable in pityriasis of the body and scalp. It removes dryness of the meatus of the ear and heals excoriation and fissures. Cotton-wool soaked in glycerin and applied to the os uteri, by causing a copious watery discharge, relieves congestion of that organ. For its hygroscopic property it forms a valuable ingredient of Cataplasma Kaolini.

Internally. **Alimentary canal.**—The lips, the tongue and the gums covered with sordes, as in acute febrile diseases, are easily cleaned by keeping them moist with glycerin. As a laxative it is not used by the mouth, but it may be combined with castor oil to render the latter less disagreeable and more effective. Glycerin (60 to 240 ms.) may be injected into the rectum by a special syringe to open the bowels in constipation. The official suppository may conveniently be used for the same purpose. The injection of glycerin is contra-indicated in piles and is useless if the faecal accumulation is very high up.

MEL DEPURATUM. (Mel. Depur.). Purified Honey.

Source.—Commercial honey melted, allowing the scum to rise to the surface, straining and adjusting, if necessary, the weight per ml. to 1.355 grm. by the addition of distilled water.

Characters.—A thick, syrupy, translucent, pale-yellow or yellowish-brown liquid. Odour, honey-like. Taste, sweet.

Composition.—A mixture of several kinds of sugar, *viz.*, cane-sugar, grape-sugar, laevulose ; also wax, pollen, colouring and odorous matters, etc.

Official Preparation

1. **Oxymel.—B. P. Dose.—30 to 120 ms. or 2 to 8 mils.**

Pharmacology and Therapeutics

Honey increases the secretions of the mouth and throat, and acts as a demulcent, relieving dryness of the mouth, cough and difficulty in swallowing. Hence it is used in gargles, cough mixtures and linctuses. It is a nutrient, and in large doses a laxative, and is therefore used to open the bowels of infants. Honey makes an excellent vehicle for castor oil and administration to new-born babes and infants.

GLYCYRRHIZA. (Glycyrrh.). **Syn.**—Glycyrrhizae Radix. *Jashthi-madhu*, Beng. *Jethi-madh*, *Mithi-lakdi*, Hind.

Source.—Liquorice consists of the dried peeled or unpeeled root and stolon of *Glycyrrhiza glabra*, and other species of *Glycyrrhiza*.

Characters.—Long, cylindrical, before being peeled dark brown, and longitudinally wrinkled ; when peeled, yellow, fibrous. Fracture, fibrous. Odour, faint, Taste, characteristic, sweet, free from bitterness.

Composition.—(1) *Glycyrrhizin*, a sweet, white, crystalline powder consisting of calcium and potassium salts of glycyrrhizic acid. Also contains *asparagin*, grape sugar, resin, starch, etc.

Enters into.—Elixir Cascarae Sagradae.

Official Preparations

1. **Extractum Glycyrrhizae.**—**B. P. Dose.**—10 to 30 grs. or 0.6 to 2 grms.
2. **Extractum Glycyrrhizae Liquidum.**—**B. P. Dose.**—30 to 60 ms. or 2 to 4 mils. **Enters into.**—The preparation of Mist. Senn. Co.

Glycyrrhizae Pulvis. (Glycyrrh. Pulv.).—Powdered Liquorice is the powder of the peeled drug.

Official Preparation

1. **Pulvis Glycyrrhizae Compositus.** *Syn.—Pulvis Pectoralis.*—Liquorice and senna leaf each 16 p.c. **B. P. Dose.**—60 to 120 grs. or 4 to 8 grms.

Pharmacology and Therapeutics

Internally.—Being sweet liquorice increases the flow of saliva. It is an excellent **demulcent**, and is largely employed in relieving sore-throat for which purpose pieces of "stick liquorice" are kept in the mouth. The dried root has no laxative effect, but pulvis glycyrrh. co. is a mild laxative owing to senna and sulphur. Liquorice makes an excellent excipient for pills and disguises the taste of many nauseous drugs.

ACACIA. (Acac.). Acacia. **Syn.**—Acaciae Gummi. *Gand*, Beng. *Babul-ka-gand*, Hind.

Source.—Acacia is the dried gummy exudation from the stem and branches of *Acacia senegal* and some other *Acacia*.

Characters.—Almost odourless ; taste, bland and mucilaginous. Rounded or ovoid tears of varying sizes, usually about 0.5 to 2.0 cm. in diameter, nearly colourless or pale yellow. Almost entirely soluble in water, yielding a translucent, viscous, slightly acid solution, insoluble in alcohol (90 p. c.).

Composition.—*Arabin* or arabic acid, combined with calcium, potassium, and magnesium. Also contains oxidising, peroxidising, and diastasic ferments.

Official Preparation

1. **Mucilago Acaciae.** *Syn.—Mucilage of Gum Acacia.*—Acacia 40 p.c.

Acaciae Pulvis. (Acac. Pulv.).—Powdered Acacia is white, colourless angular microscopic fragments, which when treated with water, rapidly diminish in size and finally disappear.

Official Preparation

1. **Pulvis Tragacanthae Compositus.**—Acacia 20 p. c. **B. P. Dose.**—10 to 60 grs. or 0.6 to 4 grms.

Non-official Preparations

1. **Injectio Sodii Chloridi et Acaciae.**—Contains 6 p. c. acacia.
2. Syrupus Acaciae—Mucilage of acacia 25, syrup to 100. *Dose.*—1 to 4 drs. or 4 to 16 mils.

Pharmacology and Therapeutics

Gum acacia is a demulcent and is given in sore-throat, catarrhal states of the gastric, intestinal or bronchial mucous membranes and in irritant poisoning. In pharmacy, it is chiefly used to suspend insoluble powders, and to emulsify resins and oils, and as an excipient for pills, jujubes, etc. The injection has been used intravenously in shock following haemorrhage (*see* page 88).

TRAGACANTHA. (Trag.). **Syn.**—Syrian Tragacanth.

Source.—Tragacanth is the dried gummy exudation obtained by incision from *Astragalus gummifer*, and other species of Astragalus.

Characters.—Thin flattened flakes, irregularly oblong, or more or less curved, marked on the surface by concentric ridges ; 2.5 cm. long and 12 mm. wide : white, or pale yellowish-white, somewhat translucent. Very tough and must be heated to 49°C. before it can be powdered. Without smell or taste. *Solubility.*—Sparingly in cold water, converts it into a gelatinous mass ; coloured violet by iodine.

Composition.—The part soluble in water consists of *Polyarabinan trigalactangeddic acid*, which on hydrolysis yields *arabinose*, *galactose*, and *geddic acid*. The insoluble portion yields *a-* and *β-tragacanthanxylanbassoric acids*, which yield on hydrolysis *tragacanthose*, *xylose* and *bassoric acid*. A little starch.

Tragacanthae Pulvis. (Trag. Pulv.).—Powdered Tragacanth is white, colourless, angular, microscopic fragments which, when treated with water, increase in size and finally disappear.

Official Preparations

1. **Mucilago Tragacanthae.—Tragacanth 1.25 p. c.**
2. **Pulvis Tragacanthae Compositus.**—Tragacanth 15 p. c. **B. P. Dose.—10 to 60 grs. or 0.6 to 4 grms.**

Non-official Preparations

1. **Linimentum Exsiccans.** *Syn.—Bassorin Paste.*—Tragacanth 5, Glycerin 2, Alcohol (90 p. c.) 10, Water to 100. Dries quickly on the skin producing a pleasant cooling sensation. May be medicated with any drug.
2. **Gelanthum** (Unna).—Heat tragacanth 2½ drs. in water 10 ozs. for 4 hours in a steam bath, press through muslin, add glycerin 6 drs. Heat on a water bath for 1 hour, add thymol water q. s. to 12 ozs.

Action and Uses.—In the form of Unna's Gelanthum, or the various "Bassorins" tragacanth is very useful in the treatment of many skin diseases. It is a demulcent, and when mixed with glycerin forms a soothing application in sore-throat but its chief use is to aid the suspension of heavy insoluble powders in mixtures. As a rule the mucilage is to be preferred to the compound powder which, on account of the starch it contains, is apt to ferment.

AMYLUM. Starch. **Syn.**—*Shetsar*, Beng.

Source.—Starch consists of polysaccharide granules, obtained from the grains of maize, *Zea Mays*, of rice, *Oryza sativa*, or of wheat, *Triticum aestivum*, or from the tubers of the potato, *Solanum tuberosum*.

Characters.—In fine, white powder or in irregular, angular masses ; odourless. Readily reduced to powder. *Insoluble* in cold water and alcohol (95 p.c.).
Incompatible.—Iodine.
Enters into.—Pasta Zinci Oxidi Co.

Official Preparation

1. **Glycerinum Amyli.—8.5 p. c.**

Action and Uses

Externally.—Starch is bland and non-irritating and may be used as a protective and absorbent in weeping eczema or excoriated and inflamed surfaces, as superficial burns. In the form of violet powder, which is merely perfumed starch, it is used to prevent excoriation of the skin of infants. Generally it is used as a basis for dusting powders and insufflations. Glycerinum amyli is a good application for chilblains and chapped hands.

Internally.—It is a food and an antidote for poisoning by iodine. Mucilage of starch (1 in 40) forms a basis for enemas and to suspend insoluble powders and oils. In the form of barley water starch is largely used as a demulcent and for diluting milk for infants.

Class C : Ointment Bases

Ointments are intended for application to the skin either for protective or emollient effect, or used as a vehicle for various solid or liquid drugs. Fats, solid or liquid hydrocarbons (paraffins), animal and vegetable oils and soaps are incorporated in their preparation as it was thought that ointments should be greasy to help penetration. It has however been realised that such greasy bases are objectionable in the treatment of wounds inasmuch as the

serous discharge provides a barrier and prevents the medicament from reaching the diseased tissue and the grease prevents the serous fluid from finding an outlet. Moreover, they prevent escape of heat from the inflamed area. To overcome these disadvantages water soluble or washable ointment bases have been introduced. Hydrous ointment, cetostearyl alcohol, sodium lauryl sulphate, emulsifying wax (lanette wax) are examples of "washable" ointment bases. When it is desired to incorporate some aqueous solution of some drugs in a greasy base, lanolin is generally selected but ointment of wool alcohols is better.

SAPO ANIMALIS. (Sap. Animal.). **Syn.**—Sodium Stearate.

Source.—Curd Soap is made from sodium hydroxide and purified solid animal fats.

Characters.—Yellowish-white or greyish-white, substance; nearly odourless; horny and pulverisable when dry, easily moulded when heated. *Soluble* in alcohol (90 p.c.), sparingly in cold, but soluble in hot water.

Enters into.—Ext. Colocynth. Co.

Sapo Durus. (Sap. Dur.). **Syn.**—Castile Soap; Olive Oil Soap; Sodium Oleate.

Source.—Hard Soap is made by the interaction of sodium hydroxide with a suitable vegetable oil or oils, or with fatty acids derived therefrom.

Characters.—A greyish-white or yellowish-white substance; nearly odourless. Becomes horny and pulverisable when dried. *Soluble* in water; almost completely soluble in alcohol (90 p.c.) and more readily soluble when warmed.

Enters into.—Ung. Zinci Oleatis.

Saponis Duri Pulvis. (Sap. Dur. Pulv.). Powdered Hard Soap.

Sapo Mollis. (Sap. Moll.). **Syn.**—Green Soap; Potassium Oleate.

Source.—Soft Soap is soap made by the interaction of potassium hydroxide, or sodium hydroxide, with a suitable vegetable oil or oils, or with fatty acids derived therefrom.

Characters.—A yellowish-white to green, or brown unctuous substance. *Soluble* in water, and in alcohol (90 p.c.).

Enters into.—Lin. Terebinthinae.

Official Preparation

1. **Linimentum Saponis.** *Syn.—Opodeldoc.*—Soap 8 p. c.

Non-official Preparation

1. **Liquor Saponis Aethereus, B. P. C.** *Syn.—Aether Soap.*—Oleic Acid 35, Caustic Potash q.s., Water q.s., Oil of Lavender 0.2, Alcohol (90 p.c.) 15, Solvent Ether to 100. For surgical use prior to operation.

Action and Uses

Soap is a **detergent** and acts by emulsifying the grease and softening the epidermis and thus helps superficial layers to be removed easily with adherent dirt. It is used to soften and remove incrustations of various skin diseases and because of its lubricating property it is utilised in the preparation of liniments. Soap makes a good basis for ointments.

Hard soap is a **gentle laxative** and corrects and aids the action of certain purgatives, such as jalap and aloe. Introduced into the rectum as a suppository it acts as a purgative and is used in constipation of infants. Soap and warm water make an effective enema for constipation of adults.

Soap is largely used in pharmacy as a basis for pills and plaster and as an emulsifying agent for the preparation of liniments, lotions and other preparations for external use.

PARAFFINUM DURUM. (Paraff. Dur.).

Source.—Hard Paraffin is a mixture of solid hydrocarbons, obtained from petroleum, or from shale oil.

Characters.—A colourless or white, translucent mass; odourless even when freshly cut, tasteless, slightly greasy to touch. Burns with a luminous flame. *Insoluble* in water and in cold alcohol (90 p.c.); soluble in solvent etner and in chloroform.

Enters into.—Ung. Alcoh. Lan., Ung. Phenol.

OFFICIAL PREPARATIONS

1. **Unguentum Paraffini.—Hard paraffin 8 p.c.**
2. **Unguentum Simplex.—Hard paraffin 10 p.c.**

Paraffinum Liquidum. (Paraff. Liq.). Liquid Paraffin.

Syn.—Liquid Petrolatum, U. S. P.; Adepsin Oil; Glymol; Oleum Deelinae; Pa[illegible].

Source.—A mixture of liquid hydrocarbons, obtained from petroleum.

Characters.—Transparent, colourless, tasteless, odourless, oily liquid. *Insoluble* in water, and in alcohol (90 p.c.); soluble in solvent ether and in chloroform.

Enters into.—Ung. Alcoh. Lan., Ung. Emulsificans.

B. P. Dose.—1/4 to 1 oz. or 8 to 30 mils.

OFFICIAL PREPARATION

1. **Emulsio Paraffini Liquidi.**—Liquid paraffin 50 p.c. **B. P. Dose.—1/4 to 1 oz. or 8 to 30 mils.**

Paraffinum Liquidum Leve.—Light Liquid Paraffin is a liquid, free from fluorescence by daylight; almost odourless when cold. *Insoluble* in water, and in alcohol (90 p.c.); soluble in solvent ether and in chloroform; miscible with fixed and volatile oils.

Paraffinum Molle Album. (Paraff. Moll. Alb.). **Syn.**—White Petroleum Jelly.

Source.—White Soft Paraffin is a mixture of semi-solid hydrocarbons, obtained from petroleum, and bleached.

Characters.—A white, translucent, soft mass; unctuous to touch. Odourless and tasteless.

Enters into.—Ung. Alcoh. Lan., Ung. Emulsificans, Ung. Hydrarg., Ung. Paraff., Ung. Phenol., Ung. Simp., Ung. Zinc. Oleat.

Paraffinum Molle Flavum. (Paraff. Moll. Flav.). Yellow Soft Paraffin. **Syn.—Yellow Petroleum Jelly.**

Source.—A mixture of semi-solid hydrocarbons, obtained from petroleum.

Characters.—A pale yellow to yellow, translucent, soft mass. Unctuous to the touch. Almost free from odour or taste. *Insoluble* in water, in alcohol (90 p.c.), soluble in solvent ether and in chloroform.

Enters into.—Ung. Alcoh. Lan., Ung. Dithranol., Ung. Hamam., Ung. Hydrarg. Nit. Dil., Ung. Paraff., Ung. Simp.

PHARMACOLOGY AND THERAPEUTICS

Externally.—Paraffins neither irritate the skin, nor become rancid, nor are they acted upon by acids, alkalies or oxidising agents. They are therefore superior to lard, and form a valuable basis for ointments meant for local action only. Hard paraffin is used to give consistence to softer ointments. As they are non-irritant and do not undergo a change by exposure to the air, they are very useful lubricating and protecting agents in psoriasis, xeroderma,

chapped hands and nipples, eczema, sunburn, etc. Paraffin forms an excellent dressing for burns. A thin film of liquid or melted paraffin is painted on the clean burn and then covered by a thin layer of cotton-wool which is covered by a second layer of paraffin. The dressing is renewed daily and is easily removed.

Internally.—Cocaine, menthol, ephedrine, etc., are dissolved in light liquid paraffin for application as a spray to the throat and in laryngeal affections. Liquid paraffin is given with the hypophosphites in the form of an emulsion as a substitute for cod-liver oil, but beyond forming a bland basis, very little is known of its effects in the tissues. Taken internally it is not absorbed, but softens and increases the bulk of the stools. It is mildly **laxative** and is largely used as a lubricant in habitual constipation, colitis, ulcerations of the bowels, etc., in ½ to 1 oz. doses. A disagreeable effect of giving liquid paraffin is that it is sometimes passed out involuntarily with the expulsion of the flatus. Repeated use may interfere with the absorption of carotene, the precursor of vitamin A.

Disadvantages.—Apart from the risk of avitaminosis, continued use of liquid paraffin as a laxative may interfere with digestion by forming a coating over the food particles and may cause loss of calcium and phosphorus. Repeated aspiration from sprays and nasal drops, and even by inhalation during swallowing, when used as laxatives specially in children, may give rise to chronic hyperplastic bronchitis or lipid pneumonia. It destroys ciliary activity of the nasal and tracheal mucous membrane.

ACIDUM OLEICUM. (Acid. Oleic.). $C_{17}H_{33}.CO_2H$. **Syn.**—Hydrogen Oleate.

Source.—Oleic Acid may be obtained by hydrolysis of fats, or of fixed oils, and separation of the liquid acids by expression.

Characters.—Colourless or yellowish, oily liquid; odour and taste, characteristic. Darkens on exposure. *Insoluble* in water, soluble in alcohol (90 p. c.), in solvent ether, in chloroform and benzene.

Enters into.—Hydrarg. Oleat., Inj. Aethanolamin. Oleat.

ACTION AND USES.—Oleic acid penetrates the skin more readily than fixed oils and fats, and is therefore used in pharmacy for compounding ointments containing metallic oxides and alkaloids. It is a **choleretic** and has been used in capsules (7½ to 15 ms.) on an empty stomach every morning in hepatic colic and to prevent formation of gall-stones.

ADEPS. Lard. **Syn.**—Adeps Praeparatus.

Source.—The purified internal fat of the hog, *Sus scrofa.*

Characters.—A soft, white, unctuous fat. Odour, faint but not rancid. *Insoluble* in water; very slightly soluble in alcohol (90 p. c.); soluble in solvent ether, in chloroform, in light petroleum.

Composition.—(1) *Olein*, 60 p. c. (2) *Stearin.* (3) *Palmitin.*

Enters into.—Ung. Hydrarg. Nit. Fort., Ung. Phenol.

OFFICIAL PREPARATION

1. **Adeps Benzoinatus.** Benzoin 2 p. c.

Adeps Lanae. (Adeps Lan). Wool Fat. **Syn.**—Anhydrous Lanolin.

Source.—It is the purified anhydrous fat-like substance obtained from the wool of sheep.

Characters.—A pale-yellow, tenacious, unctuous substance; with a characteristic faint odour. *Insoluble in water*, sparingly soluble in cold alcohol (90 p.c.), freely soluble in solvent ether and in chloroform.
Enters into.—Ung. Hamam., Ung. Hydrarg.

Official Preparations

1. **Adeps Lanae Hydrosus.** *Syn.—Lanolin.*—Wool fat 70 p. c.
2. **Unguentum Simplex.**—Wool fat 5 p. c.

Action and Uses.—Lard and wool fat are largely employed in pharmacy for making certain ointments. They are emollients. Adeps lanae is non-irritant and is readily absorbed and is therefore used as a basis for the ointment of many active drugs.

CERA FLAVA. (Cera Flav.). Yellow Beeswax. Syn. I. V.—*Mom*, Beng.

Source and Characters.—Obtained from the honeycomb of the bee, *Apis mellifica*. A yellowish-brown solid, somewhat brittle when cold, becoming plastic when warm. Odour, agreeable, honey-like. Fracture granular, not crystalline. *Solubility.*—In chloroform, and in fixed and volatile oils.
Composition.—(1) *Myricin* (melissyl palmitate), 80 p. c. (2) *Cerotic acid*, 15 p.c.

Cera Alba. (Cera Alb.). White Beeswax.

Source and Characters.—In yellowish-white solid, translucent in thin layers; made by bleaching yellow beeswax. Odour, faint, characteristic.

Action and Uses.—They are chiefly used as a basis for plasters and ointments. If the basis of the latter becomes too soft on account of the prevailing high temperature, extra white beeswax or yellow beeswax may be added to render it more suitable for use. It forms an ingredient of inj. penicillini oleosa as it delays absorption of penicillin.

ALCOHOLIA LANAE. (Alcoh. Lan.) Syn.—Hartolan Wax.

Source.—Wool Alcohols may be prepared by saponification of the grease of the wool of sheep separating the fraction containing cholesterol and other alcohols. Contains not less than 28 p.c. of cholesterol.

Characters.—Golden-brown solid, somewhat brittle when cold, becomes plastic when warm; odour, faint and characteristic. Fracture, smooth and shiny.

Official Preparations

1. **Unguentum Alcoholium Lanae.** *Syn.—Ointment of Wool Alcohols; Eucerin (Anhydrous).*—Wool alcohols 6 p. c.
2. **Unguentum Aquosum.** *Syn.—Hydrous Ointment; Eucerin (Hydrous).*—Ointment of wool alcohols and distilled water equal quantity.

Uses.—The ointment of wool alcohols, because of its cholesterol content, is miscible with its own weight of water and forms a "washable" ointment base. It is a good emulgent for water-in-oil emulsion and such emulsions do not "crack" on the addition of some weak acid, e.g. citric acid.

ALCOHOL CETOSTEARYLICUM. (Alcoh. Cetostearyl.).—

Cetostearyl Alcohol is a mixture of solid aliphatic alcohols, consisting chiefly of stearyl and cetyl alcohols. Obtained by the reduction of the appropriate fatty acids, or from sperm oils.

Characters.—A white or cream coloured unctuous mass, or almost white flakes or granules; when heated melts to a clear, colourless or pale yellow liquid free from [illegible] or suspended matter; odour, faint and characteristic; taste, bland. *Insoluble in water*; soluble in solvent ether; less soluble in alcohol (90 p. c.), and in light petroleum.
Enters into.—Cera Emulsificans.

Uses.—Cetostearyl alcohol is used chiefly for its water absorbing capacity as an emulsifying agent for either oil-in-water or water-in-oil emulsions, and forms one of the "washable" ointment bases. It forms an excellent dispersing agent for mercury and calomel ointments when used as prophylactic agents against venereal disease.

It has been found useful in chapped hand, weeping eczema and prurigo. It is used in the preparation of Penicillin Cream.

CERA EMULSIFICANS. (Cera Emulsif.). Syn.—Lanette Wax SX.—Emulsifying Wax contains cetostearyl alcohol and sodium lauryl sulphate or similar sodium salts of higher primary aliphatic alcohols.

Enter into.—Cremor Penicillini and Cremor Penicillini Sterilisatus.

OFFICIAL PREPARATIONS

1. **Unguentum Emulsificans.**—Emulsifying wax 30 p.c.
2. **Unguentum Emulsificans Aquosum.**—Emulsifying ointment 30 p.c.

SODII ET LAURYLIS SULPHAS. (Sod. et. Lauryl. Sulph.).—Sodium Lauryl Sulphate is a mixture of sodium normal primary alkyl sulphates, consisting chiefly of sodium lauryl sulphate. Contains not less than 58.0 p. c. w/w of total alcohols.

Characters.—A white, or pale yellow, powder or crystals : odour, slight but characteristic. *Soluble* in 10 parts of water, forming an opalescent solution ; partially soluble in alcohol (90 p.c.).

Enters into.—Cera Emulsificans.

Action and Uses.—Sodium lauryl sulphate is an ingredient of ung. emulsificans which has the property of remaining stable after the incorporation of most medicaments including acids, like salicylic acid. It is used as a detergent or cleansing agent, and when combined with phenylmercuric nitrate it is used as pre-operative wash-up of the skin when it inhibits the growth of gram-positive bacteria but has no effect on gram-negative ones.

GROUP XXVI

SOME MISCELLANEOUS DRUGS

ALCOHOL BENZYLICUM. (Alcoh. Benzyl.).—Benzyl Alcohol may be prepared by the alkaline hydrolysis of benzyl chloride.

Characters.—Colourless, almost odourless liquid; taste, sharp and burning. *Soluble* in 25 parts of water; miscible in all proportions with alcohol (95 p. c.) with chloroform, and with solvent ether.

Enters into.—Injectio Aethanolaminae Oleatis.

USES.—Benzyl alcohol is a local anaesthetic and is used in 1 to 4 p. c. solution by injection to produce local anaesthesia for a short period. It is added to solutions for injection to minimise pain as in Inj. Aethanolamin. Oleat. A 10 p.c. ointment or a lotion with equal parts of alcohol and water relieves pruritus.

AETHYLIS OLEAS.—Ethyl Oleate may be prepared by the esterification of oleic acid with ethyl alcohol.

Character.—A pale yellow oil. Odour and taste, strong and disagreeable. *Insoluble* in water; miscible with vegetable oils.

USES.—Ethyl oleate is used for suspension of medicaments for subcutaneous or intramuscular injeetion in place of arachis oil. It has the advantage of giving greater fluidity and thus does not require the solution to be heated before injection. It is used in the preparation of the following injections : deoxycorton. acet., menaphthoni, oestradiolis diprop., oestradiolis monobenzoatis, penicillini oleosa, progesteroni, testosteroni propionatis. Suspensions of penicillin made with ethyl oleate give a less prolonged bacteriostatic concentration than those made with arachis oil.

GROUP XXVII

SCLEROSING AGENTS

Aethnolamine, Sodium Morrhuate, Sodium Salicylate (*see* page, 466) **Quinine and Urethane** (*see* page, 489), **Glucose** (*see* page, 617).

The drugs of this group are used as sclerosing agents. They produce inflammation of the endothelial lining of the varices and are therefore largely used in the injection treatment of varicose veins. One of the most popular sclerosing agents is a combination of quinine and urethane, being very effective specially for small varices. It has however certain disadvantages : (1) it cannot be used when there is idiosyncrasy to quinine ; and (2) it is liable to produce necrosis if there is a leakage. Subsequently salicylate of soda with sodium chloride was used (*see* page 466) but it has the disadvantage of producing painful cramps in the legs or tissue necrosis. Glucose solution is also used (*see* page 619) and does not cause tissue necrosis but has not been found satisfactory because of its stickiness and the large amount required. Sodium morrhuate is largely favoured, it is usually effective and involves little risk to the patient. More recently ethanolamine in the form of injection has been found to be the most satisfactory sclerosing agent.

AETHANOLAMINA. (Aethanolamin.). **Syn.**—Monoethanolamine.—Ethanolamine is ß-aminoethanol. A clear, colourless or pale yellow liquid ; odourless ; volatile in steam. Soluble in water, and in alcohol (90 p. c.) ; sparingly soluble in solvent ether.

Official Preparation

1. **Injectio Aethanolaminae Oleatis.—B. P. Dose.—30 to 75 ms. or 2 to 5 mils by intravenous injection as a sclerosing agent.**

Action and Uses

Ethanolamine in the form of the official injection or as Ethamolin* is used in the treatment of varicose veins, and is painless, uniform in its effects and does not produce necrosis of the tissues easily, even if leakage occurs from the veins. Generally 1 to 2 mils, according to the size of the varix, is required and three or four separate sites may be injected in the same leg at a single sitting. As a rule the total quantity to be injected at one sitting should not be more than 5 mils in divided doses. This may be repeated after an interval of 5 to 7 days until the varices have been occluded.

Contra-indications.—(1) It should not be given where thrombosis has already taken place in the deep veins : (2) acute phlebitis ; (3) bed-ridden patients ; (4) when there is extensive ulceration ; (5) when there is oedema present, treatment is difficult and unsatisfactory ; (6) patient suffering from hyperthyroidism, cardiac and renal troubles ; and (7) patient suffering from skin diseases.

SODII MORRHUAS. (Sod. Morrh.). (Not official).—Sodium Morrhuate is a mixture of sodium salts of fatty acids obtained from cod-liver oil.

Characters.—Light brown granules or powder. Odour, slightly fishy but not rancid ; taste, slightly acrid. *Soluble* in water, more in warm water ; almost completely soluble in alcohol (90 p. c.).

Non-official Preparation

1. **Injectio Sodii Morrhuatis, B.P.C.**—Sodium morrhuate 5 p.c. *Dose.*—8 to 75 ms. or 1/2 to 5 mils by intravenous injection as a sclerosing agent. May undergo separation of solid matter on standing, which should be redissolved by warming, and the syringe previously warmed.

Action and Uses

Sodium morrhuate has been used as injection in the treatment of tuberculosis and leprosy but has not been a success. It is now used as a **sclerosing agent** in the treatment of varicose veins, hydrocele and varicocele. For varicose veins 1/2 to 1 mil (8 to 15 ms.) of a 5 p. c. solution is injected at each puncture, and a total of 5 mils is given spread over a fortnight. For hydrocele the sac is washed out with sterile water after the fluid has been aspirated, and 4 to 5 mils (60 to 75 ms.) of a 5 p. c. solution are injected through the

* *Ethamolin* (Glaxo Laboratories).

canula, the puncture closed with collodion and the scrotum massaged for a few minutes. A second tapping and injection is necessary, after which the scrotum becomes normal within three months. It may cause allergic reactions due to presence of impurities. It is also an irritant to the perivenous tissues if leakage occurs.

GROUP XXVIII

DIAGNOSTIC AGENTS

Class A : Drugs used for X'ray diagnosis.

1. For the alimentary canal ; **Barium Sulphate** (*see* page 108), **Bismuth Salts** (*see* page 513).
2. For the gall-bladder ; **Iodophthalein** (*see* page 384), **Phenidol** (*see* page 384).
3. For kidney affections ; **Iodoxyl** (*see* page 421) and **Diodone** (*see* page 422).
4. For lungs and bronchioles ; **Iodised Oil** (*see* page 344).

Class B : Drugs used for investigating liver or kidney functions

1. Investigation of metabolic functions of liver ; **Laevulose** (*see* page 619).
2. Investigation of renal efficiency ; **Urea** (*see* page 413), **Indigo Carmine** (*see* page 422), **Methylene Blue** (*see* page 723), **Phenol Red** (*see* page 423).

Class C : Drug used for diagnosis of corneal ulcer ; **Fluorescein** (*see* page 723).

GROUP XXIX

DRUGS WHOSE ACTIONS ARE MECHANICAL

PYROXYLINUM. (Pyroxylin.). Pyroxylin.

Source.—It is a nitrated cellulose, obtained by the action of a mixture of nitric and sulphuric acids on cotton wool (freed from fatty matter), and subsequent purification. Contains 11.5 to 12.3 p. c. of nitrogen.

Characters.—A white, matted mass of filaments, resembling cotton wool but harsher to the touch. Highly inflammable.

OFFICIAL PREPARATION

1. **Collodium Flexile.** ***Syn.—Collodion.*—Pyroxylin 2 p.c.**

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Externally.—Painted over the skin, collodion leaves a thin film from the evaporation of ether. This coating is impervious to air and moisture, and therefore causes a partial anaemia of the part by pressure on the local blood-vessels. As a *protective covering*, it may be applied to inflamed, broken or cut surfaces, chapped nipples or threatening bed-sores. It is particularly suited to scalp wounds, as by its contractile property it not only helps to draw the edges together, but does away with the necessity of a bandage. It may be employed to arrest local haemorrhage from small cuts or wounds, as in leech-bites, and to close punctured openings as in paracentesis. Mixed with salicylic acid (*see* page 465) it dissolves corns and warts. With iodoform it forms an effective pigment.

Caution.—No flame should be brought near the part until the evaporation is complete.

OLEUM THEOBROMATIS. (Ol. Theobrom.). Syn.—Cacao Butter ; Cocoa Butter.

Source.—Oil of Theobroma is a solid fat expressed from the seeds of *Theobroma Cacao.*

Characters.—A yellowish-white solid fat ; odour, slight, agreeble, resembling that of cocoa. Taste bland, characteristic. Somewhat bristle, but softness at 25°C. Melts at 30° to 35°C.

Composition.—Glycerides of *stearic, palmitic,* and *oleic acids.*

ACTION AND USES.—Because its melting point is below that of the human body, oil of theobroma is used as the basis for all suppo-

-itories which are intended to dissolve slowly when introduced into the rectum. Keep the suppositories in water till required, and put them on ice to harden before they are introduced.

GROUP XXX

COLOURING AND FLAVOURING AGENTS

Class A : Colouring agents

COCCUS. (Cocc.). Cochineal.

Syn.—*Coccus Cacti* ; *Crimidana, Cringdana*, Beng., Hind.

Source.—The dried female insect, *Dactylopius coccus* containing eggs and larvae.

Characters.—About 3.5 to 5.5 mm. long ; oval, flat, or concave beneath, convex above, transversely wrinkled ; purplish-black or purplish-grey ; easily powdered. Powder, dark red or puce-coloured.

Composition.—(1) *Carminic Acid*, 10 p. c. (2) *Fat*, 10 p. c. and wax, 2 p.c. *Carmine* is precipitated from the decoction by sulphuric acid and other reagents.

Enters into.—Tinct. Cardamomi Co., Syr. Ferr. Phosph. Co.

Official Preparation

1. **Tinctura Cocci.**—1 in 10.

Amaranthum, I. P. L. Syn.—Red No. 2.—Amaranth is the trisodium salt of 1-(4-sulpho-1-naphthylazo)-2-naphthol-3 : 6-disulphonic acid.

Characters.—Dark, reddish-brown powder. *Soluble* in about 15 parts of water at 25°C., very slightly soluble in alcohol (95 p. c.).

Caramel, I. P. L. Syn.—Burnt Sugar Colouring.—Caramel is a concentrated aqueous solution of the product obtained by heating sugar or glucose until the sweet taste is destroyed, and a uniform dark brown mass results.

Characters.—Thick, dark brown liquid with the characteristic odour of burnt sugar and a pleasant bitter taste. Miscible with water in all proportions.

Class B : Flavouring agents

Saccharin, Sucrose (*see* page 616), **Dextrose** (*see* page 617), **Glucose** (*see* page 6..), **Lactose** (*see* page 616), **Laevulose** (*see* page 619), **Honey** (*see* page 743), **Malt Extract** (*see* page 355), **Glycerin** (*see* page 742).

SACCHARINUM. (Saccharin.). **Syn.**—Gluside ; Benzosulphimide.—Saccharin is *o*-benzoicsulphimide.

Characters.—White crystals, or a white crystalline powder ; odourless, or having a faint, aromatic odour ; taste, intensely sweet, even in dilute solution. *Soluble* in 290 parts of water, in 31 parts of alcohol (95 p. c.), and in 12 parts of acetone, in about 25 parts of boiling water ; slightly soluble in chloroform and in solvent ether.

Saccharinum Sodium. (Saccharin. Sod.). **Syn.**—Soluble Saccharin ; Glusidum Soluble.—Saccharin Sodium is the sodium derivative of *o*-benzoicsulphimide.

Characters.—A white crystalline powder, odourless, or faint, aromatic odour ; intensely sweet. *Soluble* in 1.5 parts of water, in 50 parts of alcohol (95 p. c.).

Action and Uses

In large doses, saccharin is an antiseptic and passes out with the urine unaltered. It is chiefly used for its sweetening property to cover the taste of unpleasant drugs, and as a substitute for sugar in diabetes, obesity, dyspepsia, etc.

VANILLINUM.—Vanillin is 4-hydroxy-3 methoxybenzaldehyde. May be obtained from *Vanilla planifolia* or other species of *Vanilla*, or prepared synthetically. In white or cream-coloured crystalline needles or powder ; odour, and taste, characteristic of vanilla.

Uses.—Used as a flavouring agent.

PART IV

VACCINE AND SERUM THERAPEUTICS

The method by which resistance is conferred upon an animal towards a given disease forms the basis of the study of immune therapy. By *immunity* is meant non-susceptibility to a given disease or a given organism either under natural conditions or under conditions experimentally produced. By *tolerance* is meant partial or limited form of immunity. Although the term is generally applied to a condition produced after repeated use of certain drugs like opium, it is now used increasingly to denote the peculiar form of partial immunity that is developed in protozoal diseases like malaria. As a result of continued infection and reinfection with the malaria parasite a condition is established in which the host is able to live a more or less healthy life and to offer some resistance to reinfection while still harbouring the parasite in small numbers. This type of infection immunity is spoken of as '*tolerance*' or '*premunition*.'

Immunity may be classified as follows :

A. **Natural Immunity.**—This form of immunity is possessed by man and animal either from birth or acquired during growth by virtue of its species, racial or individual peculiarities. As an instance of *species immunity* may be mentioned the immunity of hens against tetanus, and of dogs, rats and mice against tuberculosis. The immunity of certain races to certain diseases, as for example, the immunity of the negro to yellow fever is considered by some as *racial immunity*. Again some families are more resistant to certain diseases than others. Certain individuals also show varying degrees of immunity to some of the infectious diseases. Natural immunity is neither absolute nor permanent. Through the administration of large doses of infective material it is possible to break this immunity. The immunity of the hen to tetanus, for example, may be overcome by giving massive doses of tetanus toxin. In the same way it is also possible to enhance natural immunity by artificial means.

B. **Acquired Immunity.**—Immunity may be acquired in two ways—*actively*, or *passively*. It is called (*i*) *active* when the individual's own tissues play an active part in the process of acquiring the resistance, and (*ii*) *passive* when the resistance is acquired through introduction from without, of ready-made protective substances or antibodies from other animals of the same or another species.

I. **Active Acquired Immunity.**—This again may arise (*a*) *naturally*, or (*b*) may be *artificially* induced.

(a) *Natural Active Acquired Immunity.*—It is well-known that an attack of an infectious disease confers upon a person a certain amount of immunity from a second attack. The immunity that is so developed is known as *natural active acquired immunity.* While in small-pox, measles, chicken-pox and plague a high degree of immunity follows an attack of the disease ; in influenza, pneumonia and gonorrhoea little or no immunity is conferred by an attack.

(b) *Artificial Active Acquired Immunity.*—Bacteria and their toxins are antigens and they stimulate the production of antibodies. In artificial active immunisation the natural process is reproduced by injecting small doses of the appropriate antigens. The following different types of antigens are used for the production of active immunisation : (i) *living virulent organism* (this is used only in animals) ; (ii) *living attenuated organisms* (as against small-pox and rabies) ; (iii) *dead suspension of killed organisms* (as against enteric fever, common cold, whooping cough, etc.) ; (iv) *toxins* (as against scarlet fever) ; (v) *toxoid, i.e.*, toxin which has been treated with formalin to destroy its toxic properties (as for immunisation against diphtheria). The term vaccination is applied to all methods of artificial active immunisation, and the material used for vaccination is known as *vaccine.*

Various terms are also used to denote *vaccine,* in which the organism is alive and not dead ; *sensitised vaccine* ; *autogenous vaccine* ; *stock vaccine* ; *polyvalent vaccine,* which is made from several strains of the same organism isolated from different cases ; *mixed vaccine* ; which is made from two or more different organisms ; *detoxicated vaccine* ; or *lipo vaccine,* which is made by suspending organisms in oil instead of saline. Vaccines are generally given, by injection in one or more doses at suitable intervals. Immunity is developed some days or weeks after the last injection, and is highly specific being effective only against the organisms used for the preparation of the vaccine. The degree and duration of immunity vary considerably in different cases. After small-pox and diphtheria vaccination, it is high and lasts a considerable time (several years) ; after a vaccination for scarlet fever, typhoid, cholera and plague it is moderate and lasts for several months ; and after vaccination for influenza, and pneumonia it is slight and lasts a very short time only. Natural active immunity confers better and more lasting protection to an individual than artificial active immunity. The latter is of very great value in the prevention of disease and of limited value in treatment.

II. **Passive Acquired Immunity.**—Passive immunisation is secured when preformed antibodies are introduced

into the tissue of a susceptible person. The antibodie are contained in the blood serum of animal which has bee rendered actively immune as the result of injection of th specific antigen. This immunity is of short duration an is of particular value in treatment—chiefly in tiding ove a crisis when antibodies are lacking in the blood of th patient. Because of rapid concentration of antibody whic can be secured very quickly after administration, this i utilised to secure immediate protection against a risk c infection, but not in anticipation of exposure on som future occasion. Active immunity takes weeks or month to develop, and is developed after injection of more tha one antigen. Once developed the protection lasts fo months or years or sometimes throughout the life.

Antisera are of three different types. When bacteri cell body itself is used in the manufacture of an ant serum the antibodies elaborated are found to have th power to agglutinate, opsonise, kill, or lyse the bacteri cell. The antiserum in this case is known as *antibacteri serum*. On the other hand if the filtered toxin of a ba terium is used for the manufacture of antiserum then th protective substances present in it have the power to ne tralise the toxins of the organisms only and in this ca the serum is known as *antitoxic serum*. In virus diseas like measles and poliomyelitis the serum of recover cases contains specific antibodies for the virus. Such se have been used for passive immunisation, and are know as *convalescent sera* or *antiviral sera*.

Bacterial toxins may be (*a*) *exotoxins*, *i.e.* poiso that are given off by the bacteria into the liquid cultu media ; they are entirely separate from the bodies of t bacteria and can be obtained in the broth after filtratio (*b*) *endotoxins*, *i.e.* poisons that are intracellular and i corporated with the other proteins in the body of the ba teria.

The diffusibility of ~~the~~ exotoxin into the cultu media has an important bearing on the production of sp cific sera. The soluble exotoxin can be separated, inject into animals, and after a time the serum of the anim contains a definite specific body—"The Antitoxin." this group belong the antitoxins of diphtheria, tetanu gas-gangrene, etc.

In the case of bacteria that only produce endotoxi the whole organism must be injected into an animal order to immunise it. The bacteria are broken down the tissues, and the endotoxin is liberated, a much weak antiserum is produced, which has a lytic action on t particular bacteria used—this serum is known as "An bacterial Serum." To this group belong the bacteric sera against the anthrax, meningococcus, pneumococcus, e

Specific antibodies.—Antibodies are specific protective substances produced by the tissue cells of the host in response to an antigen. An **antigen** is a substance, which when used parenterally is capable of causing the development of specific antibodies. Any foreign protein may act as an antigen. Antigens in common use are toxins, toxoids and bacterial vaccines.

Specific diagnosis.—In the successful treatment of a case by vaccine or serum therapy it is essential to find the causative organism or organisms of the disease. The isolated organism, if it happens to be one that forms exotoxins enables us to employ antitoxic serum as early as possible, or if one that only forms endotoxins, the bacilli can then be killed and employed as a vaccine for the immunisation of the patient from whom they were cultivated.

In the treatment of bacterial diseases either with serum or vaccine, the aim is to assist the natural forces of the body in their struggle with the invading organism, either by supplying substances which will neutralise the poisons of the invader (antitoxin), or by stimulating the cells of the body not engaged in the struggle, to manufacture antibodies.

Method of administration :—

(*a*) *Subcutaneously.*—This is the common route and is usually adopted, the best site being the loose cellular tissue of the flank or the lower abdomen, or the thigh under the fascia lata. When a large quantity is to be given, it may be injected on either side of the flank. The part is then covered with a little cotton wool soaked in collodion or Friar's balsam.

(*b*) *Intravenously.*—This route is taken in bad cases specially when the injection has been delayed. Under proper aseptic conditions there is very little risk, the serum should be diluted with three times its volume of normal saline.

(*c*) *Per rectum.*—This is done only when there is any objection to subcutaneous route. First wash out the rectum, and the serum diluted with normal saline to make the total bulk not less than 100 mils is slowly introduced into the rectum. The utility of giving serum by this route is doubtful.

(*d*) *Oral route* is sometimes recommended, although it is open to doubt whether this route is of any value except when local action in the stomach is aimed at, as for instance in the treatment of gastric or duodenal ulcer.

(*e*) *Intrathecally.*—This route is used in the treatment of cerebro-spinal fever and meningeal infections. After making a lumbar puncture, an amount of cerebro-spinal fluid equal to the bulk of serum to be injected is first drawn out, the serum is then allowed to flow by gravity from a height of 9 to 12 inches, or injected very slowly. In either case the serum should be warmed to body temperature. It is desirable to give these injections under general anaesthesia.

The production of artificial immunity is mainly what we are concerned with in this section, and will be discussed under three heads, viz.—

A. Bacteriophage Therapy.
B. Serum Therapy, or Passive Artificial Immunity.
C. Vaccine Therapy, or Active Artificial Immunity.

A. BACTERIOPHAGE THERAPY

Bacteriophage.—In 1917 d'Herelle found that the filtrates obtained from the liquid faeces of bacillary dysentery cases, when added in small quantities to young cultures of *Bact. dysenteriae* (Shiga), produced lysis of the bacteria after a period of incubation. Filtrates of these lysed cultures also showed similar lytic properties. This property was not only transmissible in series indefinitely from culture to culture but was also capable of growing in strength in each culture. From this d'Herelle suggested that the lytic agent was an ultra-microscopic virus and named it *bacteriophage*. Although the majority of subsequent workers are inclined to accept this view of d'Herelle yet there are some who believe that the lytic agent is a non-living substance of the nature of enzyme. This difference of opinion has stimulated greatly the study of phage and has led to very fruitful results. As a consequence, we are in possession of a good deal of facts regarding the properties of phage and its mode of action on bacterial organisms. Briefly, the most important properties of phage are its filtrability, its ability to multiply in the presence of young growing bacteria, its resistance to heat and alcohol, its susceptibility to acids and antiseptics, and its ability to act as an antigen. And as regards its action on organisms we know that in the presence of specific phage bacteria may get lysed, alter in virulence, change their cultural characteristics and become modified as regards antigenic properties. The organisms most susceptible to such action by phage are the members of the colon-typhoid and dysentery group and the vibrios.

The value of phage so far as the clinician and the public health worker are concerned is dependent upon its therapeutic value. In diseases like cholera and dysentery the use of a specific highly potent phage is said to be of some value both in treatment and prevention. Experiments so far carried out independently in the provinces of Madras, Assam and United Provinces, have not yielded any conclusive results. All that can be said at present regarding the value of phage in cholera is (i) that in prophylaxis there is some evidence that administration of phage helps to reduce mortality though not morbidity, and (ii) that in treatment giving of phage is better than giving no treatment, but it is not better than giving other recognised forms of treatment.

Administration of Bacteriophage.—To be of any use it should not be given with any acids or antiseptics. It acts well in an alkaline medium, therefore alkalies can be given freely, or just before its administration. It is given in doses of 2 mils, on an empty stomach diluted with a little water, either twice a day or oftener. No other drug, specially antiseptics, should be given at least one hour before and after its administration.

Bacteriophage has been prepared for typhoid, bacillary dysentery and cholera. The value of typhoid bacteriophage is doubtful and is used during the early stage of the disease. The dysentery phage is however useful in both acute and chronic cases, and gives good results when used early. Three to four ampoules should be taken daily.

B. SERUM THERAPY

Under this head are discussed the various methods by which we endeavour to cure a patient of a given disease by injecting him with the blood serum of an animal that has attained a high degree of active immunity either against the organism which is the cause of the particular disease, or against the toxin of the organism.

(a) Antitoxic Sera and Toxins

ANTITOXINA, B.P.

An Antitoxin is native serum, or a preparation from native serum, containing the antitoxic globulins or their derivatives, that have the specific power of neutralising the toxin formed by a micro-organism.

Antitoxins are prepared by separating the serum from the blood of animals which have been immunised by injections of sterile preparations from cultures of the specific organism. The native serum may be in liquid form or may be dried.

Characters.—Liquid native sera are yellow or yellowish-brown. The liquid preparations of antitoxic globulins are yellowish-brown or greenish yellow, the more highly refined preparations being almost colourless or very faintly yellow. The dried forms are yellowish-white or white powders. When reconstituted with water they resemble the original forms in colour and appearance. Liquid preparations are initially transparent but may become turbid with age.

Labelling.—The label or wrapper should state (1) the name of the product; (2) whether the product is native antitoxic serum or a preparation of antitoxic globulins in liquid or dry form; (3) the date after which the preparation is not intended for use.

The label on the container states (1) the name of the product; (2) the minimum total number of Units in the container; (3) either (*a*) the minimum number of Units in 1 mil or in grm., or (*b*) the total number of ml. or grm. of dried product, in the container.

ANTITOXINUM DIPHTHERICUM, B.P.

(Antitox. Diphtheric.)

Source.—Diphtheria Antitoxin is native serum, or a preparation from native serum, containing the antitoxic globulins or their derivatives, which have the specific power of neutralising the toxin formed by *Corynebacterium diphtheriae.*

Characters.—The serum is yellow or yellowish-brown. The antitoxic globulin solution is yellowish-brown or greenish-yellow. Both liquid forms are initially transparent, becoming opalescent in time. Almost odourless, with faint odour of the preservative. Solid forms are yellowish-white powder, or yellowish-brown flakes, and resemble liquid forms when dissolved in 10 parts of water.

Potency.—Native antitoxic serum has a potency of not less than 500 Units per mil. Dried native serum has a potency of not less than 5000 Units per grm. Preparations of antitoxic globulins have a potency of not less than 2000 Units per mil. Dried preparations of antitoxic globulins have a potency of not less than 10,000 Units per grm.

B. P. Dose.—500 to 2000 Units (Prophylactic); not less than **10,000 Units (Therapeutic) by injection.**

Action and Uses

Diphtheria antitoxin is used as a specific in the treatment of diphtheria. It neutralises the toxin elaborated by *C. diphtheriae* locally at the seat of the disease, but does not affect the vitality of the infecting organisms. The amount required as an initial dose increases with the lapse of time from the onset of disease to the time of injection. If the case is not treated until the second day, give 10,000 units; if till the third day, 12,000 units. The dose may vary from 20,000 units to even 100,000 units according to the urgency and severity of the case.

The full effect of the antitoxin is not observed till after 36 to 48 hours when used intramuscularly. Intravenous route should be utilised to secure effective concentration of antibody in the blood with minimum of delay so that the circulating toxin is neutralised immediately. For intravenous injection the serum should be diluted with three times its volume of Injection of Sodium Chloride. Another point to remember is that diphtheria is a much more fatal disease in children than to adults, and requires if anything larger doses of antitoxin. *Do not make the mistake of reducing the dose of antitoxin in proportion to the age of the patient.*

TOXINUM DIPHTHERICUM DIAGNOSTICUM, B. P. (Toxin. Diphtheric. Diagnost.). Schick Test Toxin.

Source.—It is a reagent used for the diagnosis of susceptibility to diphtheria. Obtained by preparing a sterile filtrate from a culture on nutrient broth of *Corynebacterium diphtheriae,* which, after being allowed to mature is diluted before use so that 0.2 mil contains the Test Dose. The sterile-filtrate may be diluted with a sterile solution of sodium chloride to make it isotonic with blood. It is distributed in diluted and undiluted forms in sterile containers.

B. P. Dose.—(By intradermal injection); **3 ms.** or **0.2 mil.** (Diagnostic).

Toxinum Diphthericum Calefactum, B. P. (Toxin. Diphtheric. Calefact.). Schick Control.

This is *Schick Test Toxin* heated at temperature not lower than 70°C. for not less than five minutes. It is prepared from the same batch of Schick Test Toxin as that with which it is issued for use.

B. P. Dose.—(By intradermal injection) **3 ms.** or **0.2 mil.** (Diagnostic).

TOXINUM DIPHTHERICUM DETOXICATUM, B. P. (Toxin. Diphtheric. Detoxicat.). Diphtheria Prophylactic.

Diphtheria Prophylactic is diphtheria toxin or material derived therefrom, the specific toxicity of which has been either reduced to a low level, or completely removed, by the action of chemical substances and to which diphtheria antitoxin may, or may not, have been added. It occurs in the following forms :—

(*a*) **Formol Toxoid (F.T.)**, or **Anatoxin**, a clear, faintly yellow or colourless liquid, prepared by treating diphtheria toxin, or material derived therefrom, with Solution of Formaldehyde until the toxicity is completely removed.

B. P. Dose.—The volume indicated on the label as the dose, on 2 or 3 occasions, at an interval of not less than 4 weeks in the case of two injections, and a third, if used, at an interval of not less than 2 weeks by *intramuscular or deep subcutaneous injection.*

(*b*) **Alum Precipitated Toxoid (A.P.T.)**, a suspension of white or slightly yellow particles in a colourless liquid, prepared by adding Alum to Formol Toxoid in the proportion necessary to produce a suitable precipitate, separating the precipitate, and washing and suspending it in Injection of Sodium Chloride.

Dose.—A 1st dose of **0.2 to 0.5 mil** followed at an interval of not less than 4 weeks by a second dose of **0.5 mil** by *intramuscular or deep subcutaneous injection.*

(*c*) **Purified Toxoid, Aluminium Phosphate Precipitated** (P. T. A. P.), a suspension of fine white particles in an almost colourless fluid, prepared by adding purified Formol Toxoid to a suspension of hydrated aluminium phosphate in Injection of Sodium Chloride.

B. P. Dose.—*Two doses,* each of **0.5 mil** separated by an interval of not less than four weeks by *intramuscular or deep subcutaneous injection.*

(*d*) **Toxoid-Antitoxin Floccules (T.A.F.)**, a fine suspension of white particles in a colourless liquid, prepared by adding to diph-

theria toxin a quantity of Diphtheria Antitoxin equivalent to 80 p.c. of the toxoid so produced, separating the floccules and washing and suspending them in Injection of Sodium Chloride.

B. P. Dose.—*Three doses*, each of 1 mil at an interval of not less than 4 weeks between the 1st and 2nd doses, the 3rd dose being given at an interval of not less than 2 weeks after the 2nd dose by *intramuscular injection.*

USES

Diphtheria antitoxin has been employed to confer immediate immunity in persons exposed to diphtheria and where the risk of infection is great. The usual dose is 1000 to 2000 Units irrespective of age and this gives protection for three weeks. It has however the disadvantage of rendering the patient hypersensitive to subsequent injections of serum.

A more lasting immunity is afforded by the injection of diphtheria prophylactic, of which there are several varieties, and in which the toxin has been made harmless either by combining it with antitoxin or modified to toxoid. This inoculation is not given in the presence of actual diphtheria, where immediate protection is needed, but is used in schools, asylums, hospitals, orphanages, etc., to protect against possible outbreaks. The action of all these prophylactics depends upon the fact that *C. diphtheriae* produces an exotoxin which stimulates the production of antibody when injected. The first substance used was formol toxoid (F.T.) but it has no advantage as an immunising agent over the others and the tendency to reaction following its use was considerable. Alum precipitated toxoid (A.P.T.) is generally suitable for children to whom 2 injections at one month's interval is generally given. The 1st dose is 0.2 mil and the 2nd 0.5 mil. For children over 7 years the 1st dose of 0.1 mil is preferred by many as it helps to find out individuals who are unusually sensitive to this antigen so that immunisation may be completed by the use of other available antigen. The immunising efficiency of T.A.F. (toxoid-antitoxin floccules) is high and reactions are rare, therefore it is very suitable for all ages. Its only disadvantage is that 3 injections are required instead of 2 required for A.P.T. Purified toxoid, aluminium phosphate precipitated (P.T.A.P.) has been introduced recently as a result of field trials. It is less liable to cause local reaction than alum precipitated toxoid (A.P.T.) and when injected in a single dose, it gives a consistently higher Schick conversion rate.

As a rule the prophylactic injections are given after testing the patient's susceptibility to infection with Schick Test Toxin. This is done by injecting intradermally 3 ms. (0.2 mil) of toxin on the forearm, and since the skin reaction may be due either to the specific toxin, or to nonspecific substances present, a control test is made on the

opposite arm with the Schick Control in order to exclude reactions due to non-specific substances. A positive reaction indicates that the individual is susceptible to diphtheria, and this is shown by the appearance within twenty-four to thirty-six hours of a circumscribed area of red flush. A negative reaction indicates that the subject is immune to diphtheria and is shown by the absence of reaction in the arm.

Combined Active and Passive Immunisation.—Recently a combination of antitoxin for immediate but temporary effect and A.P.T. (alum precipitated toxoid) for slow but more permanent effect have been tried with much success. Thus the disadvantage of active immunisation, which takes six to eight weeks to develop immunity, is overcome. It consists of the administration of 500 Units of antitoxin and 0.1 mil of A.P.T. as an initial dose followed after 4 weeks by a 2nd dose of 0.3 mil of A.P.T.

ANTITOXINUM TETANICUM, B.P.

Tetanus Antitoxin. (Antitox. Tetanic.)

It is native serum, or a preparation from native serum, containing the antitoxic globulins or their derivatives, which have the specific power of neutralising the toxin formed by *Clostridium tetani.*

Potency.—*For prophylactic use* : Not less than 500 Units per mil ; dried serum, not less than 5000 Units per grm. Preparations of antitoxic globulins, not less than 1500 Units per mil. Dried preparations of antitoxic globulins, not less than 7500 Units per grm.

For therapeutic use : Antitoxic globulins, not less than 3000 Unit per mil. Dried preparations of antitoxic globulins, not less than 15,000 Units per grm.

B. P. Dose.—*Prophylactic* :—Not less than **1500 Units** : *Therapeutic* : not less than **50,000 Units** *by injection.*

N.B.—The Unit is the International Unit (1950), and is equivalent to 2 International Units (1928).

Action and Uses

Since tetanus antitoxin is effective in neutralising circulating toxin, but not toxin in combination with the tissues of the central nervous system, it is largely used as a prophylactic and not therapeutic. For this purpose 1500 Units (1950) which is equal to 3000 Units (1928) should be given as soon as possible following contused or lacerated wound.

When the serum is used for curative purposes the potency should not be less than 3000 Units per mil of preparations of antitoxic globulins, and not less than 15.000 Units per grm. when dried preparations of antitoxic globulins are used. For this purpose the dose is large, 100,000 I.U. (1950) *intravenously,* followed by further doses of 25,000 I.U. every few days until symptoms abate. Intrathecal route is not recommended as it may lead to purulent aseptic meningitis or other complications.

The tetanus bacillus usually grows in the wound only for the first few days after injury, and it is during this short space of time that most of the toxin is elaborated and reaches the central nervous system. Once the symptoms of tetanus have developed, it means that the toxin has reached the nerve cells in the brain and spinal cord.

TOXINUM TETANICUM DETOXICATUM, B. P. (Toxin. Tetanic. Detoxicat.). Tetanus Toxoid.

Tetanus toxoid is tetanus toxin (the sterile filtrate of a culture on a suitable medium of *Clostridium tetani*), or material derived therefrom, the specific toxicity of which has been completely removed by the action of chemical substances in such a manner that it retains efficient properties as an immunising antigen. It may occur **in the following forms :—**

1. **Tetanus Toxoid** in simple solution is prepared by treating the filtrate with Solution of Formaldehyde. A clear, yellow or colourless liquid, free from particles.

2. **Alum Precipitated Tetanus Toxoid (A.P.T.T.)** is prepared by adding alum to tetanus toxoid in the proportion to produce a suitable precipitate. It is a suspension of white, slightly yellow or yellowish-brown particles in a colourless liquid.

B. P. Dose.—1st dose : **0.5 to 1 mil (8 to 15 ms.)** followed after an interval of not less than 6 weeks by a 2nd dose of **1 mil (15 ms.)**. *By subcutaneous* or *intramuscular injection.*

N. B. Ordinarily Tetanus Toxoid in simple solution should be supplied unless Alum Precipitated Toxoid is specified.

ACTION AND USES

A high degree of immunity to tetanus is however produced by the prophylactic use of tetanus toxoid than is obtained after the injection of a prophylactic dose of tetanus antitoxin. It is therefore used for active immunisation and the antitoxin developed persists for a long time. The immunity produced is sufficient to protect the individual from tetanus should he subsequently become infected. The use of alum precipitated tetanus toxoid resulted in complete elimination of tetanus in the Navy and Marine Corps during the World War II. The method was to use A.P.T.T. in two injections of 0.5 mil each at an interval of four to eight weeks. Sometimes a third injection is given after six months, but this is not absolutely necessary, although it remarkably increases the antitoxin much higher than is produced by the first two injections. When combined with T.A.B. vaccine, the antigenic response to the tetanus toxoid is further increased. The alum precipitated toxoid produces a persistent subcutaneous nodule.

ANTITOXINUM OEDEMATIENS, B.P.

(Antitox. Oedemat.)

Gas-gangrene Antitoxin (oedematiens) is native serum, or a preparation from native serum, containing the antitoxic globulins or their derivatives, which have the specific power of neutralising the

toxin formed by *Clostridium oedematiens.* The serum may be used in the liquid form or may be dried.

Potency.—The serum has a potency of not less than 1000 Units per mil. Dried preparation of not less than 10,000 Units per grm. Preparations of antitoxic globulins, not less than 4000 Units per mil; and of dried preparation, not less than 20,000 Units per grm.

B. P. Dose.—*Prophylactic* : **10,000 Units.** *Therapeutic* : **not less than 30,000 Units, by injection.**

Antitoxinum Welchicum, B. P. (Antitox. Welchic.).—Gas-gangrene Antitoxin (Perfringens).

It is native serum, or a preparation from native serum, containing the antitoxic globulins or their derivatives, which have the specific power of neuralising the alfa toxin formed by *Clostridium welchii.*

Potency.—The serum has a potency of not less than 300 Units per mil : and of dried preparation, not less than 3000 Units per grm. Preparations of antitoxic globulins, not less than 1200 Units per mil; and of the dried preparations, not less than 6000 Units per grm.

B. P. Dose.—*Prophylactic* : **10,000 Units.** *Therapeutic* : **not less than 30,000 Units by injection.**

Antitoxinum Septicum, B. P. (Antitox. Septic.).—Gas-gangrene Antitoxin (Septicum). **Syn.**—Gas-gangrene Antitoxin (Vibrion Septique).

It is native serum, or a preparation from native serum, containing the antitoxic globulins or their derivatives which have the specific power of neutralising the toxins formed by *Clostridium septicum,* commonly known as Vibrion Septique.

Potency.—The serum has a potency of not less than 300 Units per mil; and of dried preparation, not less than 3000 Units per grm. Preparations of antitoxic globulins, not less than 1200 Units per mil; and of the dried preparations, not less than 6000 Units per grm.

B. P. Dose.—*Prophylactic* : **5000 Units.** *Therapeutic* : **not less than 15,000 Units by injection.**

Antitoxinum Gas-gangraenosum Compositum, B.P.—Mixed Gas-gangrene Antitoxin is prepared by mixing Gas-gangrene Antitoxin (Welchii), Gas-gangrene Antitoxin (Oedematiens) and Gas-gangrene Antitoxin (Septicum).

Potency.—The sera and preparations of antitoxic globulins have a potency of not less than 1000 Units per mil for Gas-gangrene Antitoxin (Welchii and Oedematiens), and of Gas-gangrene Antitoxin (Septicum) not less than 500 Units per mil.

Dried sera and dried preparations of antitoxic globulins, not less than 5000 Units each for Welchii and Oedematiens; and not less than 2500 Units for Septicum.

B. P. Dose.—*Prophylactic* ; Gas-gangrene Antitoxin (Oedematiens) and Gas-gangrene Antitoxin (*Welchii*), not less than **10,000 Units** each; Gas-gangrene Antitoxin (Septicum), not less than **5000 Units.**

Therapeutic : Not less than **30,000 Units** each of **Oedematiens** and **Welchii** and not less than **15,000 Units** of **Septicum.**

Action and Uses

Gas-gangrene is a gangrene of the body tissues caused by the different gas-producing bacteria. It may occur from infection with three different types of organisms and the serum should be selected according to the invasion with the particular type. In severe forms, the tissue when pressed crepitates from the liberation of gas inside. Infection with these organisms is the cause of peritonitis and intestinal paralysis which follow abdominal opera-

tions ; therefore it is used as a prophylactic in acute intestinal obstruction, appendicitis, and in acute peritonitis with obstruction, when 4000 units are injected before operation intravenously, followed by intramuscular injections of smaller doses. Larger doses (10,000 units) are used for curative purposes intravenously, followed by smaller doses until the bowels act regularly.

TOXINUM STAPHYLOCOCCICUM DETOXICATUM, B. P. (Toxin. Staphylococc. Detoxicat.).—Staphylococcus Toxoid.

Staphylococcus Toxoid is staphylococcus toxin or material derived therefrom, the specific toxicity of which has been reduced to a low value by the action of chemical substances in such a manner that it retains efficient properties of an immunising antigen. May be used undiluted or diluted to a suitable strength with Injection of Sodium Chloride or other appropriate saline solution.

Characters.—The undiluted form is a pale yellow liquid, free from particles ; the diluted form is clear, colourless, or nearly colourless liquid.

B. P. Dose.—3/4 min. (0.05 mil) gradually increased to 15 ms. (1 mil) by intramuscular injection.

Uses

Staphylococcus toxoid induces production of staphylococcus antitoxin in the blood of immunised persons. It is used therapeutically for active immunisation in cases of localised infection, such as boils, carbuncles and sycosis. It is unsuitable for treatment of deep-seated infections (osteomyelitis) or septicaemia. Initial dose should not be more than 3/4 of a min. and then it should be gradually increased with the increase of the strength.

SNAKE VENOMS

Snake venom is the secretion ejected or expressed from the salivary glands of different types of snakes. It contains toxic principles which are thermostable, and coagulable proteins which are thermolabile. The main active principles are : *neurotoxin* (found in excess in cobra venom), *haemorrhagin* (found in excess in viper venom), *cytolysin*, (causes intravascular clotting). Other substances are fibrin ferment, proteolytic ferments, epithelial cells, etc.

Anti-venom Sera.—Sera which are capable of neutralising the toxic action of the venoms of poisonous snakes are prepared in different parts of the World against the venoms of local species. The Pasteur Institute, Paris, prepares four kinds for use against the venoms of snakes occurring in Europe, Africa (2) and India and Egypt.

Other anti-venom sera are prepared in India, South Africa, Australia, South America and other countries for local use.

The principle of their preparation is the same as in the case of other antitoxic sera, horses being immunised by the injection of progressive doses of solution of the dried snake venom instead of filtered bacterial toxins. Anti-venom sera are standardised accurately by determining the amount of serum required to neutralise a given quantity of venom when a mixture of the two is injected into test animals.

Dose.—100 mils or more, intravenously.

Kasauli Antivenene.—This serum is prepared against the venom of the Indian Cobra (*Naja tripudians*) and the Daboia

(*Vipera Russellii*). The preparation issued is a solution of the pseudoglobulin fraction of the serum which contains all the effective antitoxin and represents a four-fold concentration of the original serum. The antivenene is preserved by the addition of 0.35 per cent. tricresol and retains its potency for two years. Phials of 10 c.c. are issued and it is standardised to neutralise at least 2 mg. of cobra venom and 4 mg. of daboia venom per cubic centimetre.

The contents of one or two phials should be injected in the case of daboia bite and two or more in the case of cobra bite. The injections should be repeated if the symptoms do not rapidly improve. Injections should always be given intravenously when possible as the antivenene is several times more effective by this route than when given subcutaneously or intramuscularly.

Venenum Najae, I. P. L.—Cobra Venom is the dried secretion obtained from the poison glands of *Naja tripudians* and other species of *Naja*. Almost white or very light-yellow dry powder. *Soluble* in water, insoluble in methyl alcohol. Contains in 1 mg. of the dry powder not less than 50 mouse units.

N. B. A solution of cobra venom produces in presence of lecithin, haemolysis of red blood corpuscles suspended in isotonic saline (distinction from Viper Venom).

Storage.—It should be kept in all-glass containers in a cool and dry place and protected from light by wrapping with black paper.

Dose.—*By intramuscular injection* :—Initial dose, 1 to 3 mouse units. Subsequent doses, 5 to 25 mouse units or more in gradually increasing doses.

N. B. The powder should be dissolved in 1 mil of sterile water just before use.

USES.—Owing to the presence of neurotoxin and on account of its depressant action on the sensory nerve endings, it has been used as an analgesic to relieve all forms of pain specially of neuralgic nature. It is used by subcutaneous or intramuscular injection, and into the growth in malignant disease. The results have not been very encouraging and the same effect may be obtained by morphine and at a less cost. It has however been used with better result in epilepsy, although its use must be regarded as empirical. It has been suggested that the effect may be something in the nature of protein shock.

Venene.—Is alleged to be a mixture of different snake venoms, *viz.*, puff-adder venom, wight-adder venom, cobra venom and mamba venom. Useful in epilepsy and in all forms of mental disturbances.

Dose.—5 ms. subcutaneously as an initial dose increased at intervals of 2, 3, and 4 weeks to a maximum of 40 ms.

Venenum Viperae, I.P.L.—Viper Venom is the dried secretion obtained from the poison glands of *Vipera russellii* and other species of Viperae. Almost white or very light-yellow dry powder. *Soluble* in water ; insoluble in methyl alcohol. A solution of Viper Venom produces coagulation of citrated human plasma (distinction from Cobra Venom). Contains in 1 mg. of the dry powder not less than 30 mouse units.

Storage.—It should be kept in all-glass containers in a cool dry place and protected from light by wrapping with black paper.

Dose.—*By intramuscular injection* :—(Initial dose), 1 to 3 mouse units. (Subsequent doses), 5 to 25 mouse units or more in gradually increasing doses. *Should never be used for intravenous injection.*

By local application :—1 in 10,000 solution may be used as a local haemostatic.

The venom of Russell's viper has a strong coagulant action in very small dilutions. One drop of 1 in 1000 solution will clot 10 drops of haemolytic blood in 17 seconds, and a solution of 1 in 100,000 in 60 seconds. It has therefore been used as a powerful haemostatic to stop oozing of blood after operation of tonsillectomy, after extraction of tooth, in scurvy, epistaxis and haemophilia.

Stypven is Russell's viper venom for local application to control bleeding. ,The solution is prepared fresh and remains stable for seven days.

Moccasin Venom.—Moccasin snake venom is used subcutaneously or intradermally in doses of 0.4 mil of a 1 in 3000 solution. The dose is gradually increased to 1 mil and given twice a week and continued for two to three months if necessary. Since it decreases the permeability of the capillaries it has been used in purpura haemorrhagica and other forms of internal haemorrhages, *e.g.* menorrhagia but not in haemophilia.

(*b*) Antibacterial Sera

In the preparation of these sera the immunisation has been carried out by the injection of living or dead bacteria which are the cause of the disease against which it is wished to secure protection. They are not antitoxic but they are bactericidal. In addition to this there is one very important difference between antitoxic and antibacterial sera. Whereas in antitoxic sera the actual substance which neutralises the toxin is of the nature of a chemical antidote, the antibacterial sera act by neutralising the virulence of invading organisms and rendering them more susceptible to phagocytosis.

Antibacterial sera are Antimeningococcal, Anti-anthrax, Antipneumococcal, etc. These are not so efficient therapeutically as antitoxic sera and have been mostly replaced by sulpha-group of drugs and by penicillin, streptomycin and other antibiotics.

SERUM ANTIANTHRACICUM, B. P. C.—Anti-anthrax Serum consists of the serum of animals or a preparation from serum, containing certain antibodies which have a specific neutralising effect on some strains of *Bacillus anthracis.*

Dose.—20 to 40 mils *by injection.*

Action and Uses

Anti-anthrax serum or Sclavo's Serum is used both as a prophylactic and curative agent in anthrax. How it acts is not known since it does not contain any anti-toxins or bactericidins. Usually given in doses of 30 to 40 mils administered intravenously and repeated several times in the day if necessary. In an ordinary case of malignant pustule, if seen at an early stage, a single injection may be sufficient to effect a complete cure with very little loss of substance.

(*c*) Antiviral Sera

Antiviral sera are mainly of human origin, being either convalsecent sera, *i.e.* drived from persons who have acquired antibodies from exposure at some time or other to some viral infections, *e.g.* measles, or products derived therefrom.

These sera are not antitoxic, they probably act by uniting with the susceptible cells and thus prevent the specific virus from entering them thus rendering the virus inert. Once however the cells have been invaded by a virus, antisera are of no value as a curative agent, they are therefore used as a prophylactic measure.

Antiviral sera are used in the following diseases :

Measles. Convalescent serum is usually taken from otherwise normal young convalescents 6 to 9 days after the temperature has become normal. The dose is regulated by clinical trial.

The preparation generally used is human immune globulin or *gamma globulin* (prepared from pooled adult serum) which may contain about 25 times as much antibody as the adult serum from which it is prepared. The dosage of this preparation is based on the age although in America it is calculated on the weight of the patient. The results are encouraging, reactions are nil or very slight and the risk of icterogenicity is much reduced.

Mumps. Convalescent serum or preferably human immune

globulin prepared from it, may prevent orchitis provided it is given within 24 hours of onset of parotitis.

Rubella.—Human immune globulin or *gamma*-globulin prepared from convalescent serum is generally used. The dose being 4 mil to be given as soon as possible after exposure. When there is more than one exposure at intervals longer than two or three weeks a further dose should be given at each contact.

NORMAL SERUM. **Syn.**—Antilytic Serum.—It is generally prepared from the blood of healthy horse or sheep. The blood is first withdrawn and allowed to clot and when the serum separates it is collected and a small quantity of preservative (generally cresol) added. Finally it is tested to determine its haemolytic and toxic properties, and bacteriologically examined for sterility.

It contains serum globulins, serum albumin, fibrin ferment and the natural chemical substances of the blood.

Dose.—150 to 300 ms. or 10 to 20 mils.

Action and Uses

Owing to the presence of antitrypsin, which neutralises the proteolytic ferments of pus, normal horse serum is used as a local application to promote healing of old wounds and chronic ulcers. As it contains fibrin ferment it helps **coagulation of blood,** and is largely used by subcutaneous or intramuscular injection as a **haemostatic** in internal haemorrhages, *e.g.* **haemophilia,** which is believed to be due to deficiency of thrombokinase in the blood, **purpura** and in **gastric** and **duodenal ulcers** with haemorrhage. It is given orally and subcutaneously in **anaemia,** and in **debility** due to chronic diseases.

ANAPHYLAXIS

It has been observed that if an animal is injected subcutaneously or intravenously with some foreign soluble protein, whether toxic or not, it produces no symptoms at all, but a subsequent injection of the same protein, after an interval of 10 to 15 days, produces a rapid and even fatal poisoning. This reaction is specific for each protein, *i.e.* if the first injection consisted of horse serum any other animal serum will have little or no reaction. This phenomenon is known as "anaphylactic shock," and resembles those produced by the injection of peptone, or histamine. These poisoning symptoms are of the same type no matter what protein substance is given. The symptoms are a fall of temperature, constriction of bronchial muscles as evidenced by pulmonary distress and asphyxia, fall of blood pressure from relaxation of the capillaries, local urticarial reactions, stimulation of the smooth muscles, *e.g.* of the stomach, intestine and uterus, and diminished coagulability of the blood. The severity of the symptoms varies in different persons and the symptoms usually pass off in the course of an hour or two.

The term anaphylaxis was originally used to explain a condition opposite to immunity, but it is now used to designate all artificially induced conditions of hypersensitiveness in man and lower animals.

This sensitiveness to second injection remains in man possibly throughout life, and is of considerable importance in serum treatment, *e. g.* a patient who had a previous course of serum and has to be treated with it again. In case there is suspicion that the sensitive state may exist, a preliminary injection of 0.1 mil of horse serum or the serum to be used is given intradermally. If no reaction follows within one hour, the patient is nonsensitive.

Various theories have been advanced to explain the cause of this anaphylactic reaction. Friedberger suggested that the antigen combined with the antibody giving rise to precipitin, which by combining with the alexin circulating in the blood formed *anaphylotoxin*,

the cause of anaphylactic phenomena. Others again believe that the reaction is due to disturbance of the delicately adjusted colloid balance of the blood producing deposits of fibrin. Dale and Laidlaw pointed out that an injection of histamine into guinea-pigs produced symptoms similar to those of anaphylaxis, though not identical. According to them the first injection helps the formation of a new antagonistic body *precipitin*, which penetrates the cells of unstriated muscles and other tissues ; with the second injection the protein (antigen) penetrating into the cells reacts with the precipitin producing the typical symptoms.

Allergy or *hypersensitiveness* is the unnatural or exaggerated susceptibility to a substance which is harmless in similar amounts to the majority of the members of the same species. Allergy differs from anaphylaxis in that the reaction does not usually desensitise. Examples of allergy are the various food idiosyncrasies, *e. g.* appearance of urticaria, some forms of hay fever, many cases of spasmodic asthma. The nature of sensitisation may be determined in some cases by performing cutaneous inoculation with a series of protein solutions (*see* Protein Therapy, page 782).

After-effects of Sera.—Administration of sterile normal horse-serum even for the first time, sometimes gives rise to various clinical manifestations commonly known as *serum sickness*. The usual symptoms are cutaneous rashes, fever, oedema and joint pains. These generally appear between eight and fourteen days, and are avoided by the use of calcium. A concentrated serum is not likely to produce these symptoms as whole serum, due possibly to the smaller dose of the former. Serum sickness is also a form of anaphylactic phenomenon, although it is customary to call the severe, fatal and rare instances of death following the use of serum as anaphylaxis.

Treatment of Serum Disease.—This may be either for the prevention of anaphylactic shock or to combat the symptoms when the manifestations have inspite of the precautions taken appeared.

Prophylactic Treatment.—1. Calcium in the form of chloride, gluconate or lactate should be given after all therapeutic serum injections in 10 to 15 gr. doses, three or four times a day. Adrenaline (5 to 8 ms.) is always useful and may be combined with the serum, or atropine may be used.

2. The second injection may be rendered harmless by diluting it with normal saline solution in the proportion of 1 in 10.

3. *Besredka's Method of Anti-anaphylactic Vaccination.*—This consists of giving injections of small amounts of the serum before the massive injection.

Curative Treatment.—The patient should receive a purgative and kept on milk diet for a few days. If the symptoms are sudden and urgent, 4 to 6 mils of *ether* should be given intramuscularly, followed by the administration of *calcium* either by the mouth or as injection. *Atropine* hypodermically followed by injection of *adrenaline* or *ephedrine* 1/4 to 1/2 gr. by mouth. One of the antihistaminic drugs may be used (*see* page 435).

C. VACCINE THERAPY

VACCINIA BACTERIALIA.—A Bacterial Vaccine is either a sterile suspension of bacteria or a sterile extract, or derivative, of bacteria. It may be either a simple vaccine prepared from only one species, or a compound vaccine, prepared by mixing two or more simple vaccines made from different species, or varieties, of bacteria.

Characters.—They are suspensions of varying opacity, usually white, or colourless or slightly coloured liquids.

Labelling.—The label or wrapper on the package, or on the container states (1) total number of mil in the container, and (2) name and per cent. of any added bactericide or bacteriostatic.

The label on the container states (1) name of the product and (2) number of each species or variety of bacteria per mil.

A vaccine when injected into a man or animal provokes formation of immunity or antibody which directly or indirectly either destroys the infecting organisms or neutralises the toxin produced by these organisms. Vaccines may be used for the purpose of (i) *preventing diseases* (prophylactic vaccines); (ii) *curing the disease*; or (iii) *diagnosing disease.* The vaccines are essentially the same in all cases (*i.e.* bacillary emulsions), the object being to stimulate the protective mechanism of the body to form anti-substances against the particular organisms and so resist the disease.

Selection of the Organism for the Preparation of the Vaccines.—Vaccines are known as (*a*) *autogenous,* when the organism is isolated from the patient's diseased tissue grown in pure cultures and a vaccine prepared from these pure cultures; (*b*) *stock,* when the causative organism is diagnosed clinically and the vaccine prepared from a stock laboratory culture. As a general rule autogenous vaccines give the best results, but usually some delay occurs in their preparation, in such cases it may be desirable to start the treatment with a stock vaccine.

Control of Doses.—The dosage may be arrived at by considering the following factors :—

(*a*) *Toxicity of the Organism.*—The majority of the organisms we inject are highly toxic to man, *e.g.* pneumococcus, gonococcus, streptococcus, B. pyocyaneus, Bact. coli, B. Shiga, etc. and an initial dose of 5 to 10 million is ample. With organisms of low toxicity *e.g.* Salmonella typhosus, B. staphylococcus, etc., an initial dose of 100 to 500 million would not cause too violent general and local symptoms.

(*b*) *Stage of the Disease.*—In acute stages of the disease, ample toxins are already being formed and the dose should always be small.

(*c*) *Patient.—Age,* the dose can be regulated by the usual pharmacological rule of $\frac{\text{Age}}{\text{age}+12}$. *Race,* the Indian can usually stand larger doses of vaccines, other than tuberculin, which he is more sensitive to, than the European. *Colouration of the individual,* in practice one has noticed that light coloured individuals are more sensitive than the darker skinned.

(*d*) *Spacing and increasing the Dosage.*—Even when all these factors have been considered the first dose is purely an experimental one, and immunisation must be guided by watching the general, and focal symptoms. The injections are given every three or four days until the maximum dose of 1 mil of 1000 million non-toxic organism, or 1 mil of 100 million of the more toxic ones. Three or four injections at weekly intervals are given when this dose has been reached. Usually one increases by multiples of the initial dose, *viz.,* 0.1 mil, 0.2 mil, 0.4 mil, 0.8 mil, 1 mil. When injecting toxic organisms and dealing with sensitive patients, or in acute conditions, the increases should be made cautiously in half the arithmetical progression, *viz.,* 0.1 mil, 0.15 mil, 0.2 mil, 0.3 mil, 0.45 mil, 0.75 mil, 1 mil. Both the increases and the proper spacing of the dosage must be judged by local and focal symptoms. Actual harm can be done by giving too big doses whilst failure to respond may be due to employing too weak a dose. In cases that are doing well, the doses can be more rapidly increased without any harmful effects.

Immediate Effects of Vaccine

These may be local, general, or focal.

(1) *Local reaction*, this is likely to appear after a rophylactic dose, *i.e.* after a large dose. In curative reatment, when small doses are used, this reaction is as rule not observed, unless the initial dose is large. It is loubtful if local reaction has any significance.

(2) *General reaction*, as a rule prophylactic use of accine is followed by this form of reaction. For instance, rise of temperature, pains in the body or general aching, ut these should subside within twelve to twenty-four ours. In the curative treatment, provided the dose is arefully regulated, general reaction that follows the prohylactic use is rarely seen. There may be a slight rise, f temperature, say of one degree, and a general malaise. n fact the degree of general reaction is proportional to he amount used and the virulence of the bacterial endooxin.

(3) *Focal reaction.*—An exacerbation of the inflamnatory reaction, if present at the seat of the lesion, may ake place. It should be looked upon as specific and equires careful watching. This reaction should not be imed at, although a mild reaction is not necessarily preudicial to the patient.

Varieties of Vaccines

Vaccines used may be of the following kinds :—

(*a*) *Ordinary vaccine.*—It is a simple suspension of killed bacteria in normal salt solution. The bacteria are killed either by heat, r autolysis, or by some antiseptic, *e.g.* cresol.

(*b*) *Sensitised or sero-vaccines.*—These are made by bringing acterial emulsion in contact with appropriate immune serum. By his process the specific antibody in the serum becomes fixed by the acteria and this combination is termed "sensitised" vaccine.

(*c*) *Detoxicated vaccines.*—These are vaccines with the endooxin removed on the idea of introducing larger doses to get proporionately larger amount of antibody. Its practical usefulness in preerence to ordinary vaccine has not been established although many refer it.

(*d*) *Immunogens.*—This represents simple antigens almost free rom toxins and from bacterial cells. The organisms are grown on olid media suspended in salt solution and then centrifugalised ; the entrifugates forming the immunogens. Owing to their low protein ontent their use is not followed by any severe reactions and thereore can be given in larger doses. They may be used in acute and ubacute conditions.

(*e*) *Formolised vaccines.*—It has been shown that when a oxin is treated with formalin it loses its toxic properties while retaining its antigenic power, *i.e.* it ceases to be a toxin although when injected into an animal it stimulates the production of antioxin. These are known as "toxoids" in England and as "anatoxin" n France.

(*f*) *Diaplyte vaccine.*—Douglas and Fleming pointed out that hen bacteria were extracted with acetone they did not lose their ntigenic property, while some became easily dissolved in trypsin.

It was subsequently shown that a tryptic digest of the acetone extracted bacteria acted as a good antigen. Dryer "defatted" bacteria by first washing them in formalin and then extracting them with acetone. By this process the tubercle bacilli lose their acid-fast property and the streptococci and staphylococci become gram-negative, at the same time they become soluble in trypsin. Tuberc. diaplyte vaccine when injected into animals produce an anti-tuberculous serum which contains more antibodies than that produced by means of bacillary emulsion. Experience has shown that they have no special advantage over ordinary vaccines.

1. Prophylactic Vaccines

VACCINUM VACCINIAE, B.P.

(Vaccin. Vacciniae)

Vaccine Lymph is a preparation of vaccinal material obtained from the vesicles produced by inoculation of vaccinia virus on the skin of healthy animals, excluding bacterial contamination as far as possible. In viscid, colourless liquid, containing opaque white matter in suspension. The glass containers are kept at a temperature below 0° until required for issue.

N.B. It is tested to ensure compliance with tests for purity in respect of *B. anthracis*, *Bact. coli*, *Cl. tetani* and *B. haemolytic streptococci*.

The label should state date of manufacture and the conditions to be observed for maintaining the potency of the lymph.

B. P. Dose.—1 minim or 0.06 mil (by scarification).

Action and Uses

The main object of vaccination is to confer immunity against small-pox. The protection is less perfect and less permanent than an attack of small-pox. The susceptibility to small-pox after primary vaccination returns slowly and the immunity wears off after six years. Therefore re-vaccination should be done every seven years and oftener if exposed to infection. The immunity appears after one week, generally about the eighth day of successful vaccination. The vaccine virus grows and produces an enormous number of colonies at the inoculated spot by the 8th day, when the antibodies appear which attack and digest the colonies producing toxin which cause local redness and fever. Soon however the micro-organisms are killed and the contents of the pustules become inert, but antibodies remain for a long time in the body. At this period the subject remains hypersensitive, and if re-vaccinated may develop anaphylaxis.

As a rule no complication occurs if the operation is done under strict aseptic care. But cases of *post-vaccinal encephalitis* have been recorded occurring in adults previously unvaccinated. It appears 9 to 12 days after vaccination, the onset being abrupt and accompanied by headache, vomiting and drowsiness passing on to coma. It does not occur in primary vaccination of infants or in secondary vaccination. The cause of this complication is

...ction. It may be due to vaccinia virus directly, or indirectly by the activation of some unknown latent virus.

Intra-spinal, intramuscular or intravenous administration of serum from individuals who have recently been successfully vaccinated has been tried by the French physicians apparently with good results.

VACCINUM TYPHO-PARATYPHOSUM A et B, B.P.

(Vaccin. Typho-paratyphos. A et B)

Syn.—T.A.B. Vaccine.

Typhoid-paratyphoid A and B Vaccine is a sterile suspension of the bacteria *Salmonella typhi*, *Salmonella paratyphi A* and *Salmonella paratyphi B*. Contains in 1 mil 1000 million typhoid bacilli (*S. typhi*), 500 or 750 million paratyphoid A bacilli (*S. paratyphi A*,) and 500 or 750 million paratyphoid B bacilli (*S. paratyphi B*).

B. P. Dose.—*Prophylactic* :—*By subcutaneous injection* :—Alcohol-treated vaccines : **0.25** mil, initial dose ; second dose after an interval of **7 to 28 days, 0.5 mil.**

Vaccines not alcohol-treated, **0.5 mil** *initial dose* ; *second dose*, **after 7 to 28 days, 1 mil.**

Vaccinum Typho-paratyphosum A, B et C, B.P. Syn.—T.A.B.C. Vaccine.—Typhoid-paratyphoid A, B and C Vaccine is a sterile suspension of the bacteria *Salmonella typhi* 1000 million, *S. paratyphi A*, *S. paratyphi B*, and *S. paratyphi C*, each 500 to 750 million bacilli in 1 mil. It consists of vaccines prepared from strains of *S. typhi*, *S. paratyphi A*, *S. paratyphi B* and *S. paratyphi C* that are smooth and have the full complement of O somatic antigens and, in the case of *S. typhi* and *S. paratyphi C*, contain also the Vi antigen.

B. P. Dose.—*Prophylactic by subcutaneous injection* :—Alcohol-treated vaccines *initial dose*, **0.25 mil** ; *second dose*, after 7 to 28 days, **0.5 mil.**

Vaccines not alcohol-treated, *initial dose*, **0.5 mil** ; second dose, **after 7 to 28 days, 1 mil.**

Action and Uses

T.A.B. vaccine is now largely used as a prophylactic against typhoid and paratyphoid infections, and is the routine method employed in the Army and in institutions where any case of typhoid occurs. Two inoculations consisting of 0.5 mil and 1 mil are given at an interval of 7 to 28 days. There is generally some reaction after the first dose which consists of local tenderness and swelling with slight enlargement of the glands. A slight rise of temperature usually occurs with headache and general aching. In the Army in India this inoculation is repeated at intervals of 18 months. The duration of immunity is about 1 year or may be less.

Active immunisation with T.A.B. or T.A.B.C. vaccine stimulates the production by the various agglutinins appropriate to each component of the vaccine, H-agglutinins particularly in high titre. At first only vaccines of *S. typhosum* alone were used, but now the vaccines contain not only S. typhosum but also S. paratyphosum A, B and

frequently C. (T.A.B.C. should not be confused with T.A.B. Chol. formerly known as T.A.B.C.).

Alcohol treated vaccines are now largely used as in this the reaction is less and the Vi antigens remain unimpaired.

Tetanus toxoid is now incorporated with T.A.B. vaccine. It has been shown that two doses of the combined antigens (T.A.B.T.) produce satisfactory results. In fact the antibody response from the tetanus toxoid is greater than when given alone. (*See* page 763).

VACCINUM PESTIS, B. P. (Vaccin. Pest.). Syn.—Haffkine's Vaccine.—Plague Vaccine is a sterile suspension of the bacterium *Pasteurella pestis*. It contains in 1 mil 2000 million organisms (*P. pestis*).

B. P. Dose.—*Prophylactic*—1st dose, **0.5 mil** ; *second dose*, **1 mil after 7 to 21 days.**

ACTION AND USES.—When injected immunity is established in about ten days and lasts for about six months, and often longer. When once a bottle containing the vaccine is opened it should be used up as after twenty-four hours it becomes unfit for use. The results of inoculation have been distinctly satisfactory, for although absolute protection is not afforded, it diminishes not only the total number of attacks amongst the inoculated but also the percentage of mortality of those attacked.

When freshly prepared the vaccine may give rise to considerable degree of reaction and it is advised that if used within three months of the date of manufacture, the standard dose should be reduced.

VACCINUM CHOLERAICUM, B.P. (Vaccin. Choler.).—Cholera Vaccine is a sterile suspension of suitable strains of the cholera vibrio (*Vibrio cholerae*). It contains in 1 mil not less than 8,000 million bacteria (*V. cholerae*).

B. P. Dose.—*Prophylactic* : 1st dose, **0.5 mil** ; 2nd dose, after an interval of from 1 to 4 weeks, **1 mil.**

ACTION AND USES.—It takes five to six days to develop effective immunity, which is higher still after eight or ten days. The protection lasts for about six months, and this period is sufficient to help the inoculated person to tide over an existing epidemic. The local reaction is as a rule mild ; there may be oedema and painful infiltration at the site of injection, rarely followed by any systemic disturbances. The value of inoculation in controlling cholera is shown by abrupt cessation of outbreaks after systematic inoculation. The vaccine will keep in a hot climate for two years but it is desirable to use it within one year or so after preparation.

VACCINUM RABIES CARBOLISATUM, I. P. L. Syn.—Rabies Vaccine ; Pasteur Treatment ; Semple's Vaccine.—Carbolised Antirabic Vaccine is an uncontaminated suspension of brain substance

containing fixed virus of rabies, inactivated by the addition of phenol.

Characters.—A white or whitish, more or less turbid liquid having a slight odour of phenol.

Dose.—*By subcutaneous injection* :—2 to 10 mils daily for 7 to 14 days according to the site and severity of the bite.

USES

As the infecting agent in rabies cannot be cultivated on artificial media the vaccines used for anti-rabies prophylaxis are prepared from the brain and spinal cord of animals which contain the rabies virus. Pasteur found that when the virus from the dog was passaged through a series of rabbits by subdural inoculation it changed its character and became 'fixed.' The 'fixed virus' is considered not to be infective for man by inoculation into the skin or subcutaneous tissues. All anti-rabic vaccines are prepared from fixed virus and several methods of preparation are employed. Pasteur's original method, which is still in use in Paris and in other Pasteur Institutes, consisted in giving a series of doses of emulsions of spinal cord of passage rabbits subjected to desiccation for different periods. Live fixed virus is present in the Pasteur vaccine. The method in use in India, introduced by Semple, is the preparation of an emulsion of the brain and spinal cord of passage rabbits treated with 1 per cent. carbolic acid at 37°C. for 24 hours and subsequently diluted to reduce the carbolic acid to 0.5 per cent. Semple's original treatment consisted of the daily inoculation of 5 mils of a 1 per cent. emulsion for 14 days. The dosage now employed is adjusted to the estimated severity of the bite, courses of treatment varying from 7 to 21 days being given and the strength of the vaccine varying from 2 per cent. to 5 per cent. passage brain. Sheep's brain is now used for bulk production of the vaccine. As the carbolised anti-rabic vaccine does not contain living virus and retains its prophylactic value for over 6 months it is not necessary for patients to be treated at a Pasteur Institute. The vaccine can be sent out to hospitals and dispensaries where treatment is easily accessible to patients. Numerous such centres have been established in India. Neuroparalytic accidents have sometimes followed the use of anti-rabic vaccine but these are very rare with the carbolised vaccine and are seldom fatal.

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VACCINUM DYSENTERICUM (Flexner), B. P. (Vaccin. Dysenteric. (Flexner)).—Dysentery Vaccine (Flexner) contains in 1 mil 100 millions each of the V, W, X, Y, Z, types of Flexner's dysentery bacillus (*Bacillus flexneri*).

B. P. Dose.—*Prophylactic* : 1st dose, **0.5 mil** ; 2nd dose, after an interval of from 7 to 14 days, **1 mil** ; 3rd dose, after an interval of from 7 to 14 days, **1 mil.**

USES.—Its value as a preventive has not been fully established and no undue reaction has been noticed after its use.

VACCINUM FEBRIS FLAVAE, B.P.

(Vaccin. Febr. Flav.)

Yellow Fever Vaccine is a serum-free, aqueous suspension of chick embryo tissue infected with a strain of Yellow Fever virus known as 17D, which is virulent for mice, but, although avirulent for man, has retained its properties as an efficient antigen. It is supplied as a dry sterile powder, to which Water for Injection or Injection of Sodium Chloride is added immediately before administration.

Characters.—A dry cream-coloured to reddish-yellow solid which may occur as small lumps, scales or powder. Readily *soluble* in water and in saline solution.

B. P. Dose.—*By subcutaneous injection* : Not less than 500 LD 50 doses.

Action and Uses

In the preparation of this vaccine 17D strain has been chosen because its virulence is such that no dangerous or severe reaction follows its use. It has low viscerotropic and neurotropic properties. Since the strain has shown variation when kept in the laboratory, it should be carefully tested to ascertain if the viscerotropic and neurotropic properties have increased. The seed virus showing any change should be discarded. To preserve virus activity the vaccine is dried to contain only 1 p.c. moisture, but storage at 4°C. and technique of administration are equally important. Reconstituted vaccine deteriorates quickly and if not used within an hour should be discarded. As a rule, no reaction, local or general, follow the inoculation, but adrenaline should always be kept ready for the remote possibility of a severe reaction. No alcohol should be taken immediately before or after the inoculation.

The results of inoculation have been satisfactory. Aedes mosquitoes are unable to take up the virus from the blood after immunization. Mass inoculation is the only practical solution to the jungle yellow fever problem. Only one injection is necessary ; immunity appears about the 10th day and lasts for 2 to 4 years, probably longer.

VACCINUM TYPHI EXANTHIMATICI, B. P.

(Vaccin. Typh. Exanth.)

Typhus Vaccine is a sterile suspension of typhus rickettsiae which have been killed.

Characters.—A slightly turbid liquid. On prolonged standing the rickettsiae settle out as a delicate, powdery, white deposit which is readily redistributed by shaking.

B. P. Dose.—*By subcutaneous injection* ; 4 to 15 ms. or 0.25 to 1 mil.

Typhus vaccine has greatly reduced infection and also mortality among the immunized almost to nil. Two to three doses are given at an interval of 7 to 10 days.

VACCINUM PERTUSSIS, B.P. (Vaccin. Partussis).—Whooping-Cough Vaccine is a sterile suspension of *Haemophilus pertussis* in the cultural condition known as Phase I (Leslie and Gardner). Contains not less than 10,000 million and not more than 20,000 million killed phase I *H. pertussis* bacilli.

B. P. Dose.—*Prophylactic* :—Three doses, each of 10,000 million bacilli at intervals of four weeks.

The administration of this vaccine is indicated in the prevention of whooping cough. Inoculation of contacts confers some immunity against an attack and is therefore useful in controlling the spread and severity of the disease. The best time for immunisation is soon after six months. Reactions are as a rule mild, some erythema

and induration at the site of injection. Sometimes there may be fever and irritability. Since other organisms are also found as secondary invaders, a mixed vaccine consisting of pneumococcus, H. influenzae, M. catarrhalis, Staphylococcus aureus, and Streptococcus haemolyticus and non-haemolyticus is often used. Sometimes it is mixed with only Haemophilus influenzae (Pfeiffer) and pneumococcus.

2. Curative Vaccines

After the discovery of the antitoxin for diphtheria there was a rush to manufacture serums for every known bacterial disease. A few years' trial convinced the majority of medical men of the uselessness of many of these antisera, with the result that majority have disappeared in the routine treatment of disease. So it was with vaccine therapy, after the discovery by Wright of antityphoid inoculations, and the value of staphylococcus vaccines for the cure of boils, etc., a boom was started in vaccine therapy, and all and sundry were inoculated with a vaccine made from an organism that was supposed to have caused the disease.

The Limitation of Vaccine Therapy.—Immunity takes time to develop, 2 to 3 weeks; vaccines are therefore useless in acute diseases like pneumonia, and should be reserved for subacute and chronic affections. The blood fluids containing the antibodies must **have access to the causative organism.**

The uses of vaccine therapy are therefore reserved for subacute or chronic diseases; when the infective organism can readily be obtained in pure cultures; and when the antibodies produced by the graduated inoculation of these dead bacillary emulsions can come in intimate contact with the organism producing the **disease.**

VACCINUM STAPHYLOCOCCICUM, B. P. (Vaccin. Staphylococc.).—Staphylococcus Vaccine contains in 1 mil 100 million to 1000 million staphylococci (*Staphylococcus aureus*).

B. P. Dose.—*Therapeutic*: **10 million to 1000 million** organisms **at intervals of from three to seven days.**

The vaccine has proved most useful in furunculosis, folliculitis of the beard (sycosis) axilla and buttocks, in the secondary infections in acne. In sinuses where no dead bone, etc., is present, and to diminish the scar tissue after synovitis of the tendon sheaths.

Streptococcal Vaccines.—The initial dose is 5 millions increased gradually to 100 millions. The difficulty in preparing the vaccine lies (i) in getting the organism to grow on media, (ii) it is rarely found in pure cultures, and (iii) the identification of the pathogenic strains. Its greatest use is in eczematous conditions of the skin combined with staphylococcus vaccine. It is useful in erysipelas, otitis media and other streptococcal infections. It has a limited use in chronic rheumatoid arthritis, and sprue conditions of the gut.

Bact. coli.—*Dose*, 10 millions, up to 100 millions, depending on the toxicity of the strain. The initial dose should be 5 millions or less. Of great value in *infection of the bladder* and *septic cystitis* and *pyelitis* of pregnant women. Sometimes of use in *mucous colitis*. Also useful in *puerperal sepsis* when urine culture shows **growth of *Bact. coli*.**

Vaccinum Acnes, B.P. (Vaccin. Acne.).—Acne Vaccine contains in 1 mil 20 million, 100 million or 1000 million acne bacilli (***Corynebacterium acnes***).

B. P. Dose.—*Therapeutic*: **5 million to 1000 million** organisms at **intervals of from 3 to 10 days.**

TUBERCULINUM PRISTINUM, B.P.

(Tuberculin. Prist.)

Old Tuberculin is the concentrated filtrate from a fluid medium on which *Mycobacterium tuberculosis* has been grown.

Characters.—A transparent, viscous fluid ; colour, yellow to brown ; odour, like that of honey.

B. P. Dose.—*Diagnostic by intradermal injection* :—**1/6000 to 1/60 min.** or **0.00001 to 0.001 mil.**

N. B.—When Old Tuberculin is prescribed with a suffix T, the Old Tuberculin dispensed is prepared by growing the human type of bacilli. When prescribed with a suffix PT, Old Tuberculin dispensed is prepared by growing the bovine type of bacilli.

TUBERCULINI DERIVATIVUM PROTEINICUM PURIFICATUM, B.P. (Tuberculin. Deriv. Protein. Purif.). Syn.—Tuberculin P.P.D.—Purified Protein Derivative of Tuberculin is prepared by fractional precipitation with ammonium sulphate, trichloracetic acid, or other suitable protein precipitant of a fluid medium on which *Mycobacterium tuberculosis* var. *hominis* has been grown.

Characters.—A dry, cream-coloured powder, or a brown liquid. The powder form is soluble in dilute solutions of alkalies in water.

B. P. Dose.—*Diagnostic* : By intradermal injection : **0.1 mil** quantities of solutions containing, in each mil, Purified Protein Derivative of Tuberculin equivalent to 10, 100, or 1000 Units of Old Tuberculin (i.e. 1, 10, or 100 Units in each 0.1 mil injected).

VACCINUM TUBERCULINUM, B. P. (Vaccin. Tuberculin.).—Tubercle Vaccine contains in 1 mil 0.00001 to 0.1 mg. of tubercle bacilli (*Mycobacterium tuberculosis*).

B. P. Dose.—*Therapeutic* : **0.000001 to 0.1 mg.** at intervals of from three to seven days.

ACTION AND USES

Tuberculin is used chiefly as a diagnostic reagent for tuberculosis. The following are the different diagnostic methods used, *viz.*—

Von Pirquet Test or Scarification Test.—The required amount (minute drop) of old tuberculin is placed on the skin and the part scarified. In tuberculosis there is swelling and a red flush after 24 to 48 hours, when the reaction is called positive. This test is becoming obsolete.

Patch Tests.—For the Vollmer patch test old tuberculin is impregnated into the centre of a length of adhesive plaster which is closely applied to the skin of the back. In the Evan's patch test small squares of filter paper saturated with a solution of purified protein derivative of tuberculin (equivalent to 0.09 mil of O.T.) and glycerin broth as a control are applied to the cleansed skin and covered by a piece of adhesive plaster for 48 hours. The moisture of the skin dissolves the tuberculin, which is absorbed by the skin. Positive reaction is evidenced by well-defined red and indurated squares. The control area remains pale.

Tuberculin Diagnostic Jelly consists of old tuberculin

95 p.c. and 5 p.c. inert adhesive. This is applied to a cleansed area of skin and covered with a piece of gauze held in position by sticking plaster. After 48 hours the plaster is removed and the site kept under observation for one week: positive reaction is shown by reddened or slightly vesicular mark appearing in about 48 hours to 1 week.*

Intradermal Test (Mantoux.)—This consists in injecting intradermally 0.1 mil of a 1 in 10,000 or 1 in 1000 dilution of old tuberculin in normal saline. Positive reaction is indicated by the formation of a red flush with central thickening. The reaction appears between 6 to 8 hours, reaches its maximum in 24 to 48 hours. This test is very sensitive and is presumptive of active tuberculosis in children under five. In adults negative reaction excludes tuberculosis, but a positive reaction is not always indicative of active lesions.

The tubercle bacillus is said to consist of ; (*a*) a protein part which only can make the uninfected body allergic, and produce a reaction in the allergic body ; (*b*) a lipin part, which causes cell necrosis ; and (*c*) a carbohydrate part. Purified protein derivative of tuberculin is used for testing by the intradermal method. Positive reactions may be classified as follows :—

+ swelling from 5-10 mm. in diameter.
++ swelling from 10-20 mm.
+++ swelling more than 20 mm.
++++ swelling and necrosis.†

For curative purposes old tuberculin was used in very minute doses by injections, and gradually increased according to the reactions, like rise of temperature and other focal and local reactions. Its therapeutic use was found to be not without danger, and its use has been given up as being ineffective.

Preventive Inoculation

Recently much attention is being paid to the prevention of tuberculosis, and the main principles in this direction are (1) destruction of the infection, and (2) increase of individual resistance. With this object in view the following methods have been advocated to obtain immunity, *viz.*—

(*a*) *Injection of living virulent tubercle bacilli.*—This was found to be too dangerous to try on human beings.

(*b*) *Use of avirulent tubercle bacilli.*—The latest attempt to attain this object is the use of BCG vaccine (bacillus Calmette-Guerin). It is not a tuberculin but a

*Ansell and Soltys, *The Practitioner*, Sept. 1950.
† Long, Seibert and Aronson. *Tubercle*, 1935.

culture of living bovine-strain tubercle bacilli, which have been rendered avirulent. The original method of Calmette and Guerin involving culture on glycerin-bile-potato, glycerin-potato and Sauton synthetic medium have been followed at most centres with individual modifications. Whatever routine is followed in the maintenance of culture, in preparation of vaccine, and in elaborate safety controls it is important that the BCG strain should be growing rapidly when used for vaccine, so that sufficient bulk of growth is obtained while the culture is still young. Old cultures contain high proportion of dead bacilli. Vaccine prepared from slow growing cultures give unsatisfactory results.

In the preparation of the vaccine it is important that the following conditions are satisfied :—

1. Tests for safety must control (a) lack of power of BCG strain to cause progressive tuberculosis in guinea-pigs ; (b) absence of virulent tubercle bacilli from other sources ; (c) absence of other pathogenic organisms. Calmette used the vaccine after 10 days, although many modern workers have reduced this to one week. Guinea-pig inoculation of each batch is necessary to serve as a record of safety.

2. Sources of supply should be as few as practicable to ensure uniformly safe and efficient product.

3. Satisfactory method of preserving the vaccine in a fully viable state for indefinite periods so that centralisation of the preparation and completion of safety tests may be done before use.

One of the difficulties with BCG vaccine is that the organism dies rapidly and loses its immunizing potency within about 2 weeks after the vaccine has been harvested. This makes it difficult to employ adequate tests for safety, potency and sterility of the product.

Method of vaccination.—Three methods are used ; (1) *intradermal* or *intracutaneous method*, widely used in Norway ; it however sometimes produces local abscess, more rarely regional lymph-nodes may enlarge or even may suppurate ; (2) *multiple puncture* through vaccine suspension spread on the skin. This gives 100 per cent. reactors with no abscess formation. It has been extensively used in Norway and Sweden ; (3) *scarification*, used in France. Three drops of BCG suspension are placed on the skin over the deltoid and through each are made two crossed scratches 1 cm. long.

Dose.—For subcutaneous or intracutaneous vaccination generally 0.05 mg. for non-reactors is used in Norway. In Denmark, 0.1 mg. is used intracutaneously in a single dose.

Principles of BCG vaccination.—In order that BCG

vaccination may be successful and free from danger, it is essential to fulfil the following conditions :—

(a) The patients should be given tuberculin test and protected from exposure to virulent infections until they become tuberculin positive, *i.e.* until resultant immunity has developed ;

(b) no person with a positive tuberculin reaction should be vaccinated with BCG ;

(c) vaccination should be postponed if a known tuberculin-negative child is exposed to tuberculosis, until at least six weeks after exposure, and should be done only if the tuberculin reaction still remains negative.

BCG vaccination is just being tried in India but the results obtained in countries where it has been employed give significant results. Thus, while tuberculosis control programmes, exclusive of vaccination, have reduced the death-rate from tuberculosis in the U.S. from 200 to 30 per 100,000 population in the last forty years ; Denmark, during the same period, utilizing the segregation and immunisation, has reduced mortality from 300 to 32 per 100,000 population.

The BCG Advisory Committee of the State of New York reports that BCG vaccination is the only known practical method of reducing mortality and morbidity from tuberculosis. There is a general agreement that it is safe and that it serves to convert a non-reactor to tuberculin to reactor through subclinical infection with avirulent and benign bovine tubercle bacilli. It is also a general opinion that it has a significant and valuable protective effect, though the degree and duration of immunity is still somewhat uncertain.

The application of BCG vaccine on a mass scale in India can be successful if and when certain preliminary conditions are fulfilled. These include proper preparation of vaccine with safety tests of each batch, tuberculin test and subsequent segregation of those inoculated, which under the present condition appear to be not so easy.

It has been suggested that its use will prove of great value as an economically practicable measure in places where control system, as known in Western countries, may not be possible to attain for years.

BCG is a live vaccine, the virulence of which is not fixed. The use of such a vaccine presupposes the correctness of the theory that allergy due to primary infection confers some resistance against later exogenous reinfection. Many, while accepting the correctness of this doctrine, hesitate to use a live vaccine because of the risk of endogenous reinfection and uncertainty as to permanency of the attenuation.

The following observation of W. H. Bradley,* Senior Medical Officer, Ministry of Health, England, "that prophylactic use of BCG is still a controversial question, and after twenty years of trial has left the medical profession in a state of confusion as regards its efficacy" is rather interesting. Moreover the discovery of Petroff et al. (1927-28) that BCG could dissociate into virulent R and virulent S forms raised doubts regarding the use of a living vaccine although no definite case of tuberculosis has been proved to have resulted from the use of this vaccine.

PROTEIN THERAPY

Within recent years much doubt has been thrown on the specificity of the vaccines and sera used in the treatment of different diseases, since it has been found that a non-specific vaccine may sometimes be not only useful, but even act better than a specific vaccine in the treatment of a particular disease. Thus, it has been shown that some forms of gonococcus infections are greatly benefited by injections of other vaccines, *e.g.* typhoid vaccine. Upon this is based nonspecific protein therapy. It appears that the good effects observed by giving injections of peptone solutions, milk, etc., are due not so much to the presence of any specific substance, but possibly to the special kinds of foreign proteins which these injections may contain. Similarly normal horse-serum, sodium nucleinate, bacterial proteins and non-proteins like colloidal metals have been injected to provoke a reaction of the body's defensive mechanism.

The popular method of utilising protein therapy is by the injection of sterile milk, and the beneficial effects are due to the production of vaso-dilatation and consequent flooding of the diseased tissues with antibodies. Apart from milk various substances have been used to produce protein shock. They are (1) peptones in graduated doses in the treatment of bronchial asthma, urticaria, migraine, etc. ; (2) nonspecific vaccines, *e.g.* T.A.B. vaccine in acute and subacute arthritis, sciatica and general paralysis of the insane as a substitute for malarial therapy ; (3) artificially induced diseases, *e.g.* malaria in the treatment of G.P.I.; (4) blood and sera, *e.g.* autohaemotherapy in asthma, and non-specific urethritis. This is done by injecting intramuscularly 5 to 10 mils of patient's own blood ; and (5) vegetable and animal protein, *e.g.* pollen extracts.

Protein injections may be used for the following purposes :—

1. *Desensitisation.*—It has been observed that certain individuals develop asthma, hay fever, urticaria, angioneurotic oedema, etc., due to their sensitiveness or idiosyncrasies to certain proteins. Whether it is the actual food that causes the above conditions, or whether the particular foodstuff which produces within the system an anti-food protein body to which he is too sensitive, is however uncertain.

This sensitiveness to special proteins can be tested by different food products. The method followed is like doing multiple Von Pirquet's reactions, using the dried extracts in place of the tuberculin. It is generally done by scratching in regular sequence upon some surface of the body, generally the forearm, and into each successively is rubbed the product to which it is desired to test the sensitiveness of the patient. If the patient gives a strong reaction at one of the inoculated spots, it is regarded as evidence of his sensitiveness to this special substance.

* Medical Annual, 1948.

Once the case is established, the patient is treated either by avoiding the particular food substance or by producing desensitisation by injecting either a specific protein (antigen) to which he is sensitive, or by a non-specific protein like peptone or milk. The initial dose should be very small to avoid any reaction. Subsequent injections are given weekly, increasing the dose with each injection.

2. Non-specific protein when injected parenterally is followed within a short time (generally from a few minutes to one hour) by a rise of temperature, chill, sweating and leucopenia followed by leucocytosis. There is an increase of atypical erythrocytes, blood platelets, increase of fibrinogen, globulin, thrombokinase, blood sugar, non-protein nitrogen content, proteolytic ferments. Finally it increases the permeability of the cell membranes and capillaries. These reactions are more evident after intravenous injection, and after intramuscular injection in susceptible persons. Coincidently with these changes there is an increase in the antibodies and an improvement in the general condition of the patient, and a subsidence of the pain and other symptoms. The improvement is often temporary, but some patients show permanent improvement.

Protein therapy has been found efficacious in **acute** and **sub-acute arthritis, gastric** and **duodenal ulcers**. Acute **iritis** and other diseases of the eye due to local infection improve with parenteral injection of milk. The usual dose is 5 mils boiled for 4 minutes, or any of the preparations available for the purpose may be used. Similarly intragluteal injections have been used in subacute and chronic **gonorrhoeal arthritis**, sometimes with good results. **Urticaria, migraine** and attacks of **asthma** being due to hypersensitiveness to certain proteins, oral use of peptone is a simple and harmless method of checking these attacks. Injections of **Yatren-Casein, Lactolan, or Aolan** (sterile and toxin-free milk albumin) have yielded good results in gynaecological practice attended with chronic **inflammation of the appendages.**

Contra-indications.—Uncompensated cardiac lesion, acute endocarditis and pericarditis. Alcoholism is an absolute contra-indication. It should not be used in generalised or chronic multiple infection of long duration.

PART V

RADIATION THERAPY

ULTRA-VIOLET RAYS

LIGHT is caused by the periodic vibration or rotation of electrons and is the result of waves of energy transmitted through the ether. The visible light rays of the sun are composed of seven primary colours, at one end of which are the red rays and at the other the blue and the violet. In addition to these there are invisible light rays. At one end of the visible spectrum are invisible rays known as the *infra-red rays* and at the other the *ultra-violet rays*. The ultra-violet rays are the chemical rays, so called from the chemical changes they produce when projected on a sensitive medium. They are invisible light vibrations, between 400 to 100 millimicrons in length. The infra-red rays include the dark heat rays.

The composition of the rays of the sun varies with the altitude and the purity of the atmosphere. In fact the atmosphere screens off the harmful radiations. The ultra-violet rays are easily destroyed or made ineffective by moisture, dust and organic matters present in the atmosphere. In pure air there are more ultra-violet rays, so that the more purified air of mountain may contain twice as much ultra-violet rays as that of the air of the plain.

The biological action of sunlight depends upon its intensity and power of penetration and absorption. An excess of heat rays is harmful, and it is to the preponderance of heat rays that the harmful effects of the tropical sun are due. Sunlight, as is well-known, is essential to the well-being of all living beings, both animal and vegetable. But it is to the ultra-violet rays that most of the therapeutic effects of solar radiation are attributed.

The first effect of exposure is vaso-dilatation and oedema of the soft tissue, this acts as a counter-irritant and relieves congestion of the internal organs. After a latent period of four to eight hours there is erythema of the skin, although the patient may not feel anything at the time of exposure. The next effect is sterilisation of the superficial tissues. The short rays are strongly bactericidal, and these are filtered out by impurities in the atmosphere before the long rays. After a few exposures there is pigmentation of the skin which is much the same as that produced from exposure to sun's rays. This pigment protects the body against the ultra-violet rays, and after this is formed one can stand larger doses of the rays. The response of the skin to light varies, some skins being highly sensitive.

There is evidence that exposure of an infected area inhibits the growth of micro-organisms, probably by forming some germ-killing body in the infected tissue. The other important effect is the **regulation of calcium metabolism** (*see* page 99). Gates and Grant have shown that in partially parathyroidectomised animals irradiation had a definite influence in preventing tetany, and that there was a rise of serum calcium after a steep decline. It bears definite relation to body metabolism associated with parathyroid physiology, and in the absence of factors which light represents, an attempt to compensate is made by over-activity of the parathyroids.

Immense possibilities of treatment by Heliotherapy has been proved by Rollier, who exposed his patients to sun's rays in the Alps. Indeed the ideal treatment for lupus, surgical tuberculosis and rickets is by Heliotherapy at a higher altitude, where a much greater intensity of direct sunlight can be borne. But owing to the

climatic and other conditions that prevail it is not possible to practise direct sunlight treatment, except on a limited scale or in certain selected parts in India. Therefore the treatment by ultra-violet rays is done chiefly by artificial light, and electric incandescent and arc lights are largely used for the purpose. Electric lights possess properties similar to those of sunlight. The arc light is full of luminous rays but there is also a good proportion of the rays at the violet end of the spectrum and a fair amount of the ultra-violet rays. In the incandescent lamp the heat rays predominate, the ultra-violet rays are absent, being removed by the glass globe. Arons in 1892 was able to electrify mercury vapour and produce a light devoid of orange and red rays. Subsequently Cooper-Hewitt perfected this in a glass vacuum tube, so that when quartz is substituted for glass, the small amount of ultra-violet radiation given off by the incandescent lamp can be made available. The mercury vapour lamp, which is known as the "Kromayer lamp" is therefore largely used. This consists of a tube from which air has been exhausted and which is filled with mercury and mercury vapour.

The advantages of carbon arc lamp are: (*a*) the output of ultra-violet rays being small the chances of an overdosage are less and no harmful effects are observed; (*b*) for the same reason can be used for treating weak and debilitated patients in whom the use of mercury vapour lamp may be harmful; and (*c*) a large number of patients can be treated at the same time, since slight errors or timing are not attended with any signs of overdosage.

The disadvantages are: (*a*) consume a large amount of current and give off CO_2; (*b*) the electrode may burn unequally in open arc pattern; and (*c*) the output of ultra-violet rays being less the results are slow.

The ultra-violet rays only penetrate a short distance, the haemoglobin of the blood acting as a red filter screen. Under compression from surface quartz applicators or other means, the depth of penetration is increased. It is important to note that these actinic rays do not pass through glass, paper, thin cloth or ointment, but will pass through sterile water. *Vita glass* permits wave lengths up to 2000 Angstrom-units to pass through it.

The therapeutic applications of ultra-violet rays are many. Their power to cure **surgical tuberculosis** and **rickets**, to accelerate the healing of wounds and to improve the general health of weakly children has been well established. Many chronic skin diseases rebellious to other forms of treatment often yield good results when exposed to these rays, using the tungsten arc lamp. **Lupus, rodent ulcer** and **X-ray dermatitis** are successfully treated with these rays. **Septic wounds, sinuses,** and **chronic ulcers** heal quickly. Good results have been reported in the treatment of chronic **articular rheumatism, myalgia, fibrositis** and **rheumatoid arthritis**. In many depressed states of the health and **neurasthenia**, a brief exposure often gives a feeling of stimulation and a sense of well-being.

Method of administration.—This varies with the type of lamp used, the depth and extent of lesion, the power of resistance, the idiosyncrasy, and the sex of the patient. An average distance of three feet with mercury vapour lamp, and of 18 in. or less with arc lamp is considered as the average standard. The starting dose should not be more than one minute for mercury vapour lamp, and two minutes for carbon arc lamp. The following points require **careful consideration in all cases:—**

1. The eyes of both the patient and the operator must be protected by suitable goggles. Ordinary tainted or smoked glass does **not offer sufficient protection.**

2. For other parts of the body not intended for exposure, ordinary clothing affords sufficient protection

3. Children can stand relatively larger doses; women are more sensitive than men.

4. The exposure should be given once, twice or three times a week according to the condition of the trouble.

5. After continuous exposure for three months for half an hour at a time there should be a pause for several weeks.

Contra-indications.—The application is harmful to highly nervous and neurotic people and in various forms of neuritis, where it may do definite and irretrievable harm. The following conditions either contra-indicate or require modification of the dosage ordinarily given :—

1. Extremely sensitive skin.
2. Arterio-sclerosis or advanced valvular diseases of the heart.
3. Active pulmonary tuberculosis with fever. A focus of early and latent phthisis may flare up into activity through injudicious use.
4. Acute illness.
5. A tendency to haemorrhage. It should not be given in haemoptysis or in those suffering from haemophilia.
6. Chronic nephritis or quiescent appendicitis.

Untoward effects.—The belief that ultra-violet radiation is beneficial in almost any condition and that it does no harm is a mistake. While it does good in some conditions it is injurious and positively harmful in others. A common effect of overdosing, apart from that of the skin, is sleeplessness, restlessness, lassitude, loss of weight and nausea. Exposure of an extensive surface lessens resistance to bacterial infection. Eczema and many forms of skin affections are aggravated by these rays, while senile cataract has been known to follow its use when proper protection has not been taken for the eyes. A case of severe burn followed by duodenal ulcer has been recorded.

RADIUM

Radium is an element of the strontium-barium group and forms four important salts, *viz.*, bromide, chloride, carbonate and sulphate. It is constantly undergoing transformations into other substances, and becomes successively emanations of radium A, B, C, D, E, F. During these changes energy is radiated from the substance in the form of so-called *Alpha*, *Beta* and *Gamma* rays, upon the various effects of which its therapeutic action depends. Radium emanation is a gas which is scattered in the air. It is therefore put in sealed containers where emanation gradually accumulates until a maximum is reached when it is converted successively into different forms of the series. A sealed preparation of radium element or emanation emits the three types of rays, each of which has the following characters :—

The *alpha* rays travel at the rate of 18,000 miles a second, but they have very little penetrating power. As they cannot pass through a thin sheet of paper, glass, or the metal wall of the emanation containers, they have very little therapeutic value, except in the treatment of superficial lesions of the skin.

The *beta* rays travel at the rate of 60 to 180,000 miles a second and penetrate about 8 mm. of tissue, but cannot penetrate over 2 mm. of lead or 1.2 mm. of brass.

The *gamma* rays are vibrations of ether and are analogous to X-rays or ordinary light. These have greater penetrating power.

Therapeutically *beta* and *gamma* rays may be used either together or singly, the other rays being excluded by suitable screening. Certain substances (lead, silver, platinum, etc.) offer resistance to the passage of the different radium rays and these are used as screens.

Beta radiation is used chiefly in the treatment of diseases of the skin and affections of the mucous membranes, and the exposure is so regulated as to produce only definite surface radium reaction (Superficial Radium Therapy). Its action is much the same as cautery, diathermy or carbon dioxide snow.

Beta and *Gamma rays* are employed when dealing with malignant disease and morbid conditions of the pharynx and larynx, and other deep seated organs, *e.g.* the stomach, intestine, uterus, etc. (Deep Radium Therapy).

Action and Uses

Some believe radium to be the most expensive and efficient form of cautery as yet discovered, while others maintain that it has a marked selective action in destroying pathological tissues without affecting normal tissue. The effect varies with different growths **and even in normal tissues.**

Radium emanation if of sufficient intensity and acts for sufficient length of time has three distinct effects on the living cell, *viz.*—(1) Increase of cell activity with possibly associated proliferation; (2) arrest of cell activity; and (3) degeneration and destruction of cell. The effects are not apparent immediately after exposure. Generally 1 to 2 days or even 2 to 3 weeks pass before any change is observed. This latent period varies with the strength of the source of energy and the amount of filtration and protection used.

Because of its destructive effect on certain forms of tumour cells, the chief application of radium is found in surgery. Although it cannot replace surgery, some permanent cures of superficial cancer of the skin of the basal-celled type have been recorded when properly treated. Rapidly growing cellular types of malignant disease often show at least a temporary set-back. As a palliative in subduing haemorrhage, relieving pain, arresting discharge and offending odour and in prolonging life at least temporarily, its value **is undisputed.**

It has been successfully used in **rodent ulcers, epitheliomata** of the skin and **keloids,** while some cases of successful treatment of tumours of the brain are also recorded. In **lymphomas** and **Hodgkin's disease,** application of radium reduces the size of the involved glands, but whether any permanent cure is effected is doubtful. Similarly improvement has been noticed in both **simple** and **exophthalmic goitre.**

Its use in the treatment of cancer of the **rectum** is followed by good results, but do not justify its use as a substitute for operation. The best results are obtained in **epithelioma** of the anus and in the low growths of the posterior wall. Its use in the **carcinoma** of the **breast** has been followed by remarkable results and it is now recognised that early cases can be treated as successfully by radium as by operation. In the treatment of **carcinoma** of the **cervix uteri,** "split doses" or repeated treatment at brief intervals as recommended by Heymann of Stockholm is generally followed. In borderline and inoperable cases, radium is the method of choice and gives better results than X'rays. In **fibroma** and **fibromyomata** of the uterus, its use has been attended with encouraging results.

Method of Application

The main principle underlying all radium therapy is the correct estimation of dosage and exposure necessary to bring about the death of pathological cell without markedly affecting the function and vitality of the normal ones. An insufficient dose may act as a stimulus and thus aggravate the condition; while an over-dose may destroy normal tissue. The source of radiation should be standard-

ised under the exact conditions in which it is to be employed. The duration, the amount of radio-active element, filtration, distance, and susceptibility of the skin and the general vitality of the patient demand careful consideration. The intensity and quality of the rays depend on the amount of radio-active substance, the distance from the patient and the filtration used, while the effects depend on the rays absorbed by the tissue. The dose for surgical use is usually from 50 to 200 mg. For superficial skin lesions smaller doses are used, while for large deep-seated growths larger doses are necessary.

Methods of administration.—For therapeutic purpose radium may be applied in the following ways :—

1. *In platinum tubes or needles.*—This prevents the *alpha* and *beta* rays. Each tube contains 2 to 3 mg. of radium with 0.5 to 0.8 mm. of platinum screening. This gives quite good results.

2. *Radon seeds.*—Radium emanation or radon is a gas soluble in water, which can be stored in small tubes or seeds. These seeds are minute needles of gold or platinum which contain minute glass tubes of radium emanation. These seeds are inserted in diseased tissues with special form of cannula and left permanently there. They are therefore of special use in the treatment of diseases of the abdominal cavity where one can be inserted and left inside, thus avoiding another operation. They cease to give off rays after ten days.

Acute constitutional symptoms follow surface and distance therapy with large quantity of radium than with interstitial radiation. Malaise, headache, nausea, and diarrhoea are generally observed. Irradiation of the upper abdomen is often followed by more severe constitutional disturbance than of head, neck, or pelvis.

Local changes in those handling radium are chiefly due to *alpha* and *beta* rays, and produce blunting of sensation of the finger tips, paraesthesia and anaesthesia, thickness of the epidermis and chronic dermatitis. If injury is severe, healing rarely occurs ; hair follicles, sebaceous and sweat glands disappear. Telangiectasis and pigmentary changes with chronic ulcertions may also take place.

The *constitutional disturbances* have been attributed to cellular destruction and consequent protein absorption. Patients already in toxic condition are more susceptible to radium sickness. The mechanism by which tissue destruction provokes these symptoms is not fully understood. They may be a form of anaphylaxis or may be due to diverse metabolic changes at different stages of irradiation.

The following points should be noted in the therapeutic use of radium, *viz.*—

(1) That its intensity varies with the length of exposure. A short exposure causes stimulation of the tissues, a longer exposure inflammation, and a prolonged exposure destruction of the cells.

(2) That healthy cells react to radiation in proportion to their rate of growth. Lymphatic organs, hair follicles, glands of the skin, testicles and ovaries are particularly sensitive and are easily destroyed ; while cartilage, bone, muscle, connective and nerve tissues are resistant to radiation. Diseased cells are more readily destroyed than healthy ones.

(3) That malignant cell and the cells of a more rapidly growing tumour are more easily affected by radiation than normal ones.

RADIOACTIVE ISOTOPES

Within recent years radioactive substances are being used for (1) experimental purposes ; and (2) therapeutic trials.

For *experimental purposes* they are used in pharmacological research to investigate absorption, clearance, storage and distribution of different substances either in the human body or in animals. The substance under investigation is "tagged" with a radioactive

isotope which acts as a "tracer" substance since it can be detected in the body by virtue of the radiation which it emits. Different methods are used for the detection of radio isotopes in the body tissues and fluids both in health and disease. One method is by measuring the radiation emitted by means of Geiger-Müller counter. Another method is by auto-radiograph. A section of the radioactive material in tissues is placed in close apposition to a photographic plate and the ß-rays emitted help development of the photoactive substance in the plate. This enables localisation of radioactive **material in tissues.**

Radioactive iron (Fe_{59} prepared by bombarding ordinary iron, Fe_{58}) has been used as a "tracer" substance to follow its absorption and distribution in the body (see page 665). It has been possible to calculate the rate of clearance of iodine from the blood by administration of radioactive iodine. Combined with fluorescein, radioactive iodine (I_{131}) has been used to diagnose and localise brain tumours. That the reticulo-endothelial system is concerned in the formation of antibody has been established by the application of **radioactive phosphorus.**

For *therapeutic purposes* radioactive iodine has been used in the treatment of hyperthyroidism (see page 712) and radioactive phosphorus in the treatment of leukaemia and polycythaemia (see **page 132).**

What is Radioactive Isotope ?

All chemical elements are composed of three essential constituents, namely, protons which carry positive, electrons negative and neutrons no electric charge. Protons and neutrons constitute the nucleus and electrons surround the nucleus. Since neutrons carry no charge and pass through an electric field without deflection, they are suitable for bombarding the nuclei of atoms. The mass of protons and neutrons is about the same, i.e. contains one atomic unit each, but that of electron is much less. The atomic weight of an element depends upon the total number of protons and neutrons it contains, while its atomic number, hence its chemical properties, depends on the number of peripheral electrons and protons, carrying negative and positive charges respectively. It follows that the chemical properties of an element will remain unaltered even though its atomic weight is changed. Thus, two or more atoms may have the same chemical properties, the same atomic number but different atomic weights. Different atomic forms of the same element are known as *isotopes.* Since their electron shells are the same, isotopes possess the same chemical properties, but their differences in atomic weight are associated with certain different physical properties. It has therefore been possible to administer an isotope, for example, iron, which can be distinguished physically from all other iron in the body, yet which will be mobilised chemically in exactly the same manner as **normal iron.**

Isotopes can be produced by bombardment methods of modern nuclear physics, when they become radioactive. Red phosphorus, for instance, of atomic weight 31 (P_{31}) captures a neutron and acquires an atomic weight of 32. This is radioactive phosphorus **(P_{32}) and emits ß-rays.**

PART VI

INDIAN INDIGENOUS DRUGS

Expectorants and Bronchial Antispasmodics

VASAKA, I. P. L. Syn.—*Bakas,* Beng. *Adulsa,* Hind.

Source.—The fresh and the dried leaves of *Adhatoda vasica.*
Composition.—(1) *Vasicine,* a crystalline alkaloid. (2) An *organic acid* (Adhatodic acid). (3) *Ammonia.*
Dose.—15 to 30 grs. or 1 to 2 grms.

PREPARATIONS

1. **Extractum Vasakae Liquidum, I. P. L.**—Vasaka in No. 40 powder 20 grm., alcohol (60 p.c.) q.s. to produce 20 mils. *Dose.*—15 to 30 ms. or 1 to 2 mils.
2. **Syrupus Vasakae, I. P. L.**—Liquid extract 50, glycerin 10, syrup q. s. to 100. *Dose.*—30 to 60 ms. or 2 to 4 mils.

PHARMACOLOGY AND THERAPEUTICS

Internally.—Both the leaves and roots are stimulant **expectorants** and **bronchial antispasmodics.** The root may be used as a substitute for senega. It is an excellent remedy for **chronic bronchitis, phthisis** and **bronchial asthma.** It acts by virtue of vasicine which relaxes the bronchial muscles by depressing the vagus endings (Chopra and S. Ghosh). The decoction of the root bark is frequently used in catarrh, mild fever and bronchitis. It is useful in mild forms of **pertussis,** especially when complicated with bronchitis. The leaves smoked in the form of cigarettes relieve **asthma,** as they evolve ammoniacal vapour when burnt. The syrup forms a vehicle for cough mixtures.

SAUSSUREA, I. P. L. Syn.—The Costus ; Kut.

Source.—The dried roots of *Saussurea lappa,* with pungent aromatic odour and a pungent taste.
Composition.—(1) *Saussurine,* an alkaloid. (2) An aromatic oil. (3) Resin tannin, bitter substances, inulin, etc.

PREPARATION

1. **Tinctura Saussureae I. P. L.—Saussurea in powder 2000 grm., alcohol (90 p. c.) q. s. to make 1000 mils. *Dose.*—15 to 60 ms. or 1 to 4 mils.**

ACTION AND USES

Kut has been used in India as a **tonic, antiperiodic** and **aphrodisiac.** The essential oil is an antiseptic and is eliminated by the genito-urinary tract which it stimulates. It is possible that the aphrodisiac effect is due to local irritation. Saussurine causes **relaxation** of the **bronchial muscles** partly by direct action on the muscle, and partly through the vagus (Chopra). The essential oil acts as an expectorant while excreted through the bronchial mucous membrane. It is therefore largely used in the treatment of **bronchial asthma,** and as an **expectorant** in the form of the tincture either alone or with other expectorants like potassium iodide. It is also used as a **carminative** and **diuretic.**.

Laxatives

BELAE FRUCTUS, I. P. L.—Bael.

Source.—The fresh unripe or half-ripe fruit of *Aegle marmelos.*
Composition.—(1) *Marmelosin,* the important active principle. (2) Tannin. (3) *Pectin. Mucilaginous principles,* sugar, etc.

PREPARATION

1. **Extractum Belae Fructus Liquidum, I.P.L.**—Bael. bruised 1000 grm., chloroform water 15000 mils, chloroform 2 mils, alcohol (90 p.c.) q.s. to 1400 mils. *Dose.*—60 to 120 ms. or 4 to 8 mils.

PHARMACOLOGY AND THERAPEUTICS

Internally.—The pulp of the ripe fruit is a **laxative**, and is valuable in spastic and **chronic constipation**. The pulp may be taken itself or may be made into a sherbet by soaking in water and then straining it. A little sugar may be added if required. The unripe pulp roasted, or a decoction made from the unripe slices dried in the sun (*Bael suti*) is astringent and is therefore used in **mucous diarrhoea** and **dysentery**. As a demulcent and mild laxative the ripe fruit may be used during convalescence from **dysentery** and early stage of **sprue**. The compound or dietetic bael powder (powdered pulp 1, arrowroot 1) may be used in the same class of cases. The ripe pulp is very serviceable in obstinate **catarrhal diarrhoea**, and **chronic dysentery**.

Drastic Purgatives

TURPETHUM, I. P. L. Syn.—Indian Jalap ; *Teuri*, *Dudhiva-Kalmi*, Beng. *Pithori*, Hind.

Source.—The dried root and stem of *Ipomaea turpethum*.

Composition.—(1) A resin, *Turpethin*. The root contains 5 to 10 p.c. (2) A fatty substance. (3) A volatile oil. (4) Albumin, starch, yellow colouring matter, lignin, salts and ferric oxide.

Dose.—15 to 45 grs. or 1 to 3 grms.

PREPARATIONS

1. **Pulvis Turpethi Co., I. P. L.**—Turpeth 7, potassium acid tartrate 7, ginger 1. *Dose.*—60 to 90 grs. or 4 to 6 grms.
2. **Tinctura Jalapae Composita, B. P. C.**—Jalap 80 grms., scammony resin 15 grms., turpeth 10 grms., alcohol (60 p. c.) *q. s.* to 1000 mils. *Dose.*—30 to 60 ms. or 2 to 4 mils.

PHARMACOLOGY AND THERAPEUTICS

As a **purgative** it is *equal to jalap* and *superior to rhubarb* ; it has moreover a great advantage over both these drugs in that it is free from nauseous smell and taste. It also acts very efficiently when given alone. It is often necessary to give it in larger doses than jalap, but this is no disadvantage. It has been in use in India as a **cathartic** from a very early date. When combined with chebulic myrobalans, it is useful in **dropsy**. The usual method of administration is to rub down about a drachm of the root or stem with water and add to it some rock-salt and ginger, or sugar and pepper.

KALADANA, I. P. L. Syn.—Pharbitis Seeds. *Nilkalmi*, Beng.

Source.—The dried seeds of *Ipomaea hederacea*.

Composition.—*Pharbitsin*, a resin, about 8 p.c. It resembles the resin of Jalap (*convolvulin*), and corresponds to it in chemical properties. *Fixed oil*, 12 p.c. mucilage, tannin.

Dose.—30 to 45 grs. or 2 to 3 grms.

PREPARATION

1. **Pulvis Kaladanae Compositus, I. P. L.**—Kaladana, 7 ; acid potassium tartrate, 7 ; ginger, 1. *Dose.*—60 to 90 grs. or 4 to 6 grms

Kaladanae Resina. Syn.—Pharbitisin.

Source.—A mixture of resins obtained from Kaladana. In brownish opaque fragments, translucent at the edges , brittle, breaking with a resinous fracture of a disagreeable odour, specially when warmed.

Dose.—2 to 8 grs. or 0.12 to 0.5 grm.

PHARMACOLOGY AND THERAPEUTICS

The action and uses of kaladana and its resin are the same as those of jalap (see page 377), but it is a milder remedy. In small doses it is a gentle purgative, but in large ones, especially in the form of Pulv. Kaladanae Co. it has a drastic action and can be used with benefit in all cases of dropsy.

Bitters

KALMEGH, I.P.L. Syn.—Andrographis ; Creat ; Kiryat.

Source.—Kalmegh is the dried or fresh entire aerial portion of the plant *Andrographis paniculata.* It yields not less than 1 p.c. *andrographolide.*
Composition.—A bitter principle andrographolide ; tannic acid ; sodium chloride.

Preparation

1. **Extractum Kalmegh Liquidum, I.P.L.**—Prepared with alcohol (90 p.c.) to contain not less than 0.5 p.c. andrographolide. *Dose.*—8 to 15 ms. or 0.5 to 1 mil.

Action and Uses.—Kalmegh is a bitter and is used chiefly in children's ailments, action being almost similar to quassia. It has a reputation of being valuable in children suffering from torpidity of the liver and constipation.

ARISTOLOCHIA, I.P.L. Syn.—Indian Birthwort ; *Isharmul,* Beng.

Source.—Aristolochia consists of the dried stem and root of *Arisitolochia indica.*
Composition.—A bitter principle, a volatile oil which probably contains borneol, tannin, starch.

Preparation

1. **Tinctura Aristolochiae, I.P.L.**—1 in 5 of alcohol (70 p.c.). *Dose.*—30 to 60 ms. or 2 to 4 mils.

Action and Uses.—It is a bitter and may be used as such in place of gentian or serpentary. In large doses it causes vomiting and purging.

TINOSPORA, I.P.L. Syn.—*Gulancha,* Beng. and Hind.

Source.—Tinospora consists of the dried stems with the bark intact of *Tinospora cordifolia,* collected in hot season.
Composition.—Berberine, a bitter substance, starch, etc.

Preparation

1. **Tinctura Tinosporae, I.P.L.**—1 in 5 of alcohol (60 p.c.). *Dose.*—30 to 60 ms. or 2 to 4 mils.

Action and Uses.—Tinospora is a pure bitter without tannin and may be used in place of other bitters like quassia and calumba. It has a reputation of being antiperiodic and is used for the purpose in chronic malarial fever with iron and small doses of quinine.

Diuretics

PUNARNAVA, I.P.L. Syn.—*Punarnaba,* Beng. ; *Shothagni,* Sans.

Source.—Consists of fresh or the dried plant of *Boerhaavia repens,* or the leaves of the white variety of *Trianthema portulacastrum,* known in Bengali as *Sabuni.*
Composition.—(1) An alkaloid *Punarnavine,* 0.01 p.c. ; (2) Potassium nitrate, 0.2 p.c.

Preparation

1. **Extractum Punarnavae Liq., I. P. L.**—Punarnava in coarse powder 2000 grms., alcohol (60 p.c.) and water each q.s. to make 1000 mils. *Dose.*—30 to 120 ms. or 2 to 8 mils.

Action and Uses

Punarnava has been used in India as a remedy for dropsy from time immemorial. Intravenous injection of the alkaloid in animals produces a distinct and persistent rise of blood pressure and marked **diuresis.** The diuresis is chiefly due to the action of punarnavine on the renal epithelium, and partly to the rise of blood pressure. The presence of a large amount of nitrate of potassium contributes to the diuresis when the liquid extract is used. It is very valuable in cases of dropsy due either to **cirrhosis of the liver,** or when associated with **kala-azar,** and **ascites** due to chronic peritoneal condi-

tions. It is not of much value in cardiac dropsy or in chronic nephritis when given alone, but combined with other diuretics it increases the amount of urine. It loses its action after a few days when its use should be stopped.

Urinary Antiseptics

CUBEBAE FRUCTUS. **Syn.**—Cubebs ; *Kabab chini*, Beng.

Source.—The dried full-grown unripe fruits of *Piper Cubeba*.

Composition.—(1) The *volatile oil*, 10 to 18 p.c. (2) *Cubebin*, **a neutral body.** (3) A resin-containing *cubebic acid*. (4) *A fatty oil*. Gum.

Dose.—30 to 60 grs. or 2 to 4 grms.

Preparation

1. **Oleum Cubebae.**—A pale green, greenish-yellow or colourless oil, smelling of cubebs, distilled from cubebs. *Dose.*—5 to 20 ms. or 0.3 to 1.2 mils.

Pharmacology

Internally. **Gastro-intestinal tract.**—The action of cubebs resembles that of pepper. In small doses it is a **stimulant, stomachic** and carminative, and in large doses it **impairs digestion** and causes **gastro-intestinal irritation.**

Respiratory **and genito-urinary tracts.**—Like many oleoresins cubebs stimulates the secretions of the mucous membranes of the **respiratory** and **genito-urinary passages** and renders them aseptic. **It** is a **diuretic** and **genito-urinary antiseptic.**

Elimination.—It is chiefly excreted in the bronchial secretion and urine, and is probably found in the latter in the form of a salt of cubebic acid, which may be precipitated by nitric acid. Many of the specific germs are destroyed by the products of the volatile oil **as they pass out.**

Therapeutics

Internally.—Unlike copaiba, cubebs is often used in the form of lozenges or inhalation to relieve **cough, cold** and **sore-throat.** On account of its specific action on the genito-urinary passages, it is used in acute or chronic **gonorrhoea, gleet** and **cystitis.**

Prescribing **hints.**—The powdered cubebs may bé given in lozenges, cachets, and the oil in capsules, or in emulsion, often with **buchu, etc.**

Antiperiodics

BERBERIS, **I.P.L.** **Syn.**—*Daruharidra*, Beng. *Darhald*, Hind.

Source.—The dried roots of *Berberis aristata*. **Contains not less than 1 p.c. berberine.**

Composition.—The chief alkaloids are (1) *Berberine*, and (2) *Oxycanthine*. **Tannin, resin, gum, etc.**

Dose.—30 to 45 grs. or 2 to 3 grms.

Berberinae Sulphas, **I.P.L.** (Berberin. Sulph.).—Berberine Sulphate is the acid sulphate of an alkaloid, berberine, obtained chiefly **from** ***Berberis aristata*** **and** ***Coptis teeta.***

Characters.—Bright yellow acicular crystals or dark yellow powder ; **taste,** bitter. *Soluble* in water (1 in 100) and in alcohol (90 p.c.).

Dose.—1 to 5 grs. or 0.06 to 0.3 grm.

Preparations

1. **Tinctura Berberidis. I. P. L.**—Berberis 200, alcohol (60 p. c.) q. s. 1000 mils. ***Dose.*—30 to 60 ms. or 2 to 4 mils.**
2. **Extractum Berberidis. I. P. L.**—A semisolid watery extract from the roots of several species of berberis sold under the name of **Rasaut.** *Dose.*—1/2 to 1 gr. **or 30 to 60 mg.**

Pharmacology and Therapeutics

Externally.—Being a mild local astringent, *rasaut* is employed with benefit as a pigment around the eyes in acute and chronic

ophthalmia. Berberine in dilution of 1 in 80,000 is toxic to **Leishmania tropica,** and it has been used successfully in **oriental sore** either in the form of the extract, or berberine sulphate 1 mil of a 1 to 2 p.c. solution may be infiltrated into the margins of the sores by means of a fine hypodermic syringe, once a week.

Internally.—Berberine is a stimulant to the gastro-intestinal tract and acts as a stomachic in small doses. It is a **diaphoretic** and **antiperiodic** and has been used in the treatment of malaria, either alone or in combination with quinine. It is doubtful, however, whether it has any specific effect on the parasites, and the results have been disappointing. It however helps to expel the parasites into the peripheral circulation and acts as a provocative agent in the diagnosis of malaria.

Given intravenously the alkaloid causes a fall of blood pressure from dilatation of the splanchnic vessels and cardiac depression.

ALSTONIA. **Syn.**—Dita Bark. *Saptaparna,* Sans. *Chatim,* Beng. *Chatian,* Hind.

Source.—The dried bark of *Alstonia scholaris* and of *Alstonia constricta.*
Composition.—The bark contains many alkaloids, the chief being *ditamine, echitamine* or *ditaine* from the *dita bark* (*A. scholaris*) and *Alstonine* and *porphyrosine* from the bark of *A. constricta.*

Preparations

1. **Infusum Alstoniae.**—1 in 20. *Dose.*—1/2 to 1 oz. or 15 to 30 mils.
2. **Tinctura Alstoniae.**—1 in 8. *Dose.*—30 to 60 ms. or 2 to 4 mils.

Pharmacology and Therapeutics

The bark is an astringent, tonic, antiperiodic, and anthelmintic, being considered very useful in chronic **diarrhoea,** advanced stages of **dysentery** and **catarrhal fevers.** Ditaine paralyses the motor nerve-endings in mammals. It has been used successfully in the treatment of **malarial fever,** either alone or with small doses of quinine. It enhances the value of quinine.

PICRORHIZA, I.P.L. **Syn.**—*Kutki, Katki,* Beng., *Katuka* Sans.

Source.—The dried rhizome of *Picrorhiza Kurroa.*
Composition.—(1) Bitter glycoside, *Picrorhizin,* yielding as its decomposition product *picrorhizetin* and *dextrose.*

Dose.—10 to 20 grs. or 0.6 to 1.2 grms. as a tonic ; 45 to 60 grs. or 3 to 4 grms. as an antiperiodic.

Preparations

1. **Extractum Picrorhizae Liquidum, I. P. L.**—1 in 1 of alcohol (60 p. c.). *Dose.*—15 to 60 ms. or 1 to 4 mils.

2. **Tinctura Picrorhizae Co., I. P. L.**—1 in 10. Picrorhiza, dried sweet-orange peel, cardamom, alcohol (45 p. c.). *Dose.*—30 to 60 ms. or 2 to 4 mils.

Pharmacology and Therapeutics

The root is bitter and stomachic and is often used whenever a bitter is indicated, as in **dyspepsia** and **neuroses** of the stomach and bowels. It is an **antiperiodic,** and is used in malarial fever in place of, or with, quinine. Because of the presence of cathartic acid it acts as a gentle cathartic when given alone, and in large doses acts as a purgative. As a remedy for **bilious fever** *kutki* is often combined with various aromatics.

Volatile and Fixed Oils

CUMINUM, I.P.L. Cumin. **Syn.**—*Jira,* Beng. Cumin is the ripe fruit of *Cuminum cyminum.*

Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

Oleum Cumini, I.P.L.—Oil of Cumin is the oil distilled from the fruits of *Cuminum cyminum.*

Characters.—Colourless or pale yellow when fresh, becoming darker on keeping. Odour, characteristic, unpleasant; taste, spicy, somewhat bitter. *Soluble* in 11 volumes of alcohol (80 p. c.).

Dose.—2 to 4 ms. or 0.12 to 0.25 mil.

Action and Uses.—The oil and the fruits are used as carminatives in the form of aromatic water. The fruit is also used in cookery. Its chief constituent is *cumic aldehyde* which can be artificially converted into thymol.

OLEUM CASSIAE, I.P.L.—Oil of Cassia is the volatile oil distilled with steam from the leaves and twigs of *Cinnamomum cassia.*

Characters.—Yellowish or brownish oil, becoming darker and thicker on keeping; odour and taste, characteristic. *Soluble* in an equal volume of alcohol (95 p. c.), and in 2 volumes of alcohol (70 p. c.).

Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

PREPARATIONS

1. **Aqua Cassiae Conc., I. P. L.** *Dose.*—5 to 15 ms. or 0.3 to 1 mil.
2. **Aqua Cassiae Destillata, I.P.L.** *Dose.*—1/2 to 1 oz. or 15 to 30 mils.
3. Spiritus Cassiae.—1 in 10 of alcohol (95 p.c.). *Dose.*—8 to 16 ms. or 0.5 to 1 mil.

Action and Uses.—The same as oil of cinnamon.

OLEUM CINNAMOMI FOLII, I. P. L.—Cinnamon Leaf Oil is the oil distilled from the leaves of *Cinnamomum cassia*, and other species of *Cinnamomum.* Contains from 70 to 90 p. c. v/v of Eugenol, $C_{10}H_{12}O_2$.

Characters.—A dark brown liquid. Odour, penetrating, fragrant, resembling those of cinnamon and clove; taste, very pungent.

Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

Action and Uses.—The same as those of cinnamon and clove.

OLEUM CINNAMOMI FOLII, I. P. L.—Cinnamon Leaf Oil is Verbena; *Gandha Benar tel.* Beng.—Oil of Lemon Grass is the oil distilled from *Cymbopogon citratus*, and *Cymbopogon flexuosus.*

Characters.—Dark yellow oil. Odour resembling that of verbena. Almost entirely soluble in 3 parts of alcohol (70 p.c.).

Composition.—*Citral*, an optically inactive aldehyde, 75 to 85 p.c. Also traces of geraniol, methylheptenone, traces of citronellal, possibly linalol.

Dose.—1/2 to 3 ms. or 0.03 to 0.2 mil.

Action and Uses.—Externally it is a rubefacient like cajuput and may be used mixed with some bland oil as embrocation in lumbago, myalgia, chronic rheumatism, etc. It disguises the smell of iodoform and is largely used in perfumery.

OLEUM GAULTHERIAE, I. P. L. Syn.—Oil of Wintergreen.—Oil of Gaultheria is the oil distilled from the fresh plant, *Gaultheria fragrantissima.* Contains not less than 98 p.c. of esters calculated as methyl salicylate, $CH_3C_7H_5O_3$.

Characters.—Colourless or nearly colourless oil. Odour, strong, characteristic; taste, pungent.

Dose.—5 to 15 ms. or 0.3 to 1 mil.

Action and Uses.—Oil of Wintergreen is absorbed by the unbroken skin and is used for external application in chronic rheumatic affections, fibrositis, and lumbago. It may be painted over the part and covered over by oil silk and bandaged or the oil may be mixed with some bland oil and used as liniment. It is a very popular remedy for application in the treatment of pain of neuralgic character like sciatica, etc. In fact most of the proprietary analgesic preparations contain it. It may also be used internally in capsules. (*See* methyl salicylate, page 467).

OLEUM PUDINAE, I. P. L.—Pudina Oil is the oil distilled from the fresh leaves of *Mentha arvensis.* Contains 75 p. c. of Carvone, $C_{10}H_{14}O$.

Characters.—A transparent deep [illegible] liquid. Odour, characteristic; taste, pungent and aromatic.

Dose.—1 to 3 ms. or 0.06 to 0.2 mil.

Preparations

1. **Aqua Pudinae Conc. I.P.L.**—*Dose.*—5 to 15 ms. or 0.3 to 1 mil.
2. **Aqua Pudinae Destillata, I.P.L.**—*Dose.*—1/2 to 1 oz. or 15 to 30 mils.
3. **Spiritus Pudinae, I.P.L.** *Syn.—Essence of Pudina.*—1 in 10 of alcohol (90 p. c.). *Dose.*—8 to 16 ms. or 0.5 to 1 mil.

Action and Uses.—It resembles oil of peppermint in action and is used as a flavouring agent and carminative.

OLEUM AJOWAN, I. P. L. Syn.—Ptychotis Oil. *Jowaner tel,* Beng. *Ajowan ke tel,* Hind.

Source.—The oil distilled from the fruit of *Carum copticum.*

Characters.—Colourless ; odour and taste of thyme. If cooled to 15.5°C. should yield not less than 40 p.c. of crystalline *thymol,* known in the Indian bazaars as *ajowan ke phool.*

Dose.—1/2 to 3 ms. or 0.03 to 0.2 mil.

Pharmacology and Therapeutics

Internally.—The action and uses of the oil resemble those of thymol (*see* page 701). The fruit when chewed removes the nauseous taste of drugs and the oil corrects the griping of purgatives. **Omum water** or *ajowan ke arak,* distilled from the fruits, is a valuable **carminative** and **antispasmodic in colic** and **flatulent dyspepsia.** Ajowan is often chewed with *pan,* or taken with salt for indigestion.

PSORALEAE SEMINA, I. P. L. Syn.—*Babchi,* Beng.

Source and Characters.—The seed of *Psoralea corylifolia,* brownish-black, 3 to 4.5 mm. long 2 to 3 mm. wide ; flattened and oblong. Odour, aromatic ; taste, bitter, pungent.

Composition.—An *essential oil,* a fixed oil, and a resin.

Preparation

1. **Linimentum Psoraleae. I.P.L.** *Syn.—Babchi Ointment.*—It is an oleo-resinous extract obtained from the powdered seeds.

Action and Uses

It has been used as a remedy for **leucoderma.** The oleo-resinous extract (which contains most of the volatile oil) is a suitable preparation which is rubbed over the diseased patches. It should be diluted with fresh olive oil according to requirements.

OLEUM SINAPIS EXPRESSUM, I. P. L. Syn.—Mustard Oil. —Expressed Oil of Mustard is obtained by pressure from the seeds of *Brassica juncea.*

Characters.—A brownish-yellow to golden yellow clear liquid. Odour, characteristic ; taste, pungent. Slightly soluble in alcohol.

Action and Uses.—Expressed oil of mustard is extensively used in cookery specially in Bengal. It has a mild rubefacient properties and is used mixed with camphor and liquor ammonia as embrocation to the chest or other parts of the body.

Astringent

MYROBALANUM, I. P. L. Syn.—Chebulic Myrobalans. *Haritaki,* Beng. *Hara,* Hind.

Source.—The dried fruits of *Terminalia Chebula.*

Composition.—(1) *Tannic acid,* about 20 to 40 p.c. (2) *Gallic acid,* (3) Resin.

Dose.—30 to 60 grs. or 2 to 4 grms.

Preparations

1. **Unguentum Myrobalani, I. P. L.**—1 in 4 of paraffin ointment.
2. **Unguentum Myrobalani cum Opio, I.P.L.**—7.5 p.c. of opium.

Action and Uses

These fruits are powerful **astringents, stomachics** and **tonics.** The finely powdered fruit forms an important ingredient of tooth powder and is a valuable remedy for **spongy** and **ulcerated gums.**

Paradoxical as it may appear the dried unripe fruit acts as a gentle laxative. One or two fruits taken daily at bed-time keep the bowels very regular, giving one or two evacuations in the morning. On account of the astringent and aperient properties, myrobalans, especially the smaller variety (*Jangi haritaki*), are very useful in diarrhoea and dysentery. Owing to the large amount of tannin which they contain, they are of great service as lotions and injections and may be substituted with advantage for galls. The ointment is a valuable application in piles. They may also be chewed with benefit to remove the after-taste of nauseous drugs.

Antidysenteric

KURCHI, I.P.L. Syn.—Conessi Bark. *Kurchi*, Beng. *Kutaja*, Sans.

Source.—The dried bark of *Holarrhena antidysenterica*.

Composition.—The seed and the bark contain three alkaloids (1) *Kurchicine* or *Conessine*, an amorphous powder, soluble in water and alcohol and in dilute acids. (2) *Holarrhenine*. (3) *Kurchine*. Also contains tannin.

Dose.—8 to 15 grs. or 0.5 to 1 grm.

Preparation

1. **Extractum Kurchi Liquidum, I.P.L.**—Contains 1 p.c. w/v of the total alkaloids of kurchi. *Dose.*—180 to 240 ms. or 12 to 16 mils.

Kurchi et Bismuthi Iodidum, I. P. L. Syn.—Anabin ; Kurchibin. —Kurchi Bismuth Iodide is a combination of bismuth iodide with the total alkaloids of kurchi. Contains 23 to 27 p.c. total kurchi alkaloids and 18 to 24 p. c. of bismuth.

Characters.—Fine reddish-orange to dark-red powder ; odourless ; taste, bitter and acrid. Sparingly *soluble* in water.

Dose.—5 to 10 grs. or 0.3 to 0.6 grm.

Action and Uses

Kurchi is a well-known remedy for the treatment of **dysentery** both acute and chronic. It acts by virtue of the alkaloid *kurchicine* which has a specific action on *E. histolytica*. Before the value of ipecacuanha was recognised in dysentery it was the only remedy extensively used in India. It may be given alone, in the form of liquid extract or may be combined with small doses of castor oil, extract of bael, or decoction of isaphgul, or the seeds (*indrajab*) may be given in the form of powder with powdered isaphgul seeds. Kurchicine may be used subcutaneously in 1/2 to 1 gr. doses, but as it depresses the heart and makes it irregular it cannot be used intravenously. It has no effect on the pregnant uterus in therapeutic doses and therefore may be given safely during pregnancy (Chopra). Kurchi--bismuth-iodide is used in cases of chronic intestinal amoebiasis with better results than with pure kurchi preparations and has the advantage over similar preparation of emetine in not being a depressant. The alkaloid may be used in the same conditions and is free from any cumulative effect. Sometimes flushing of the face and extremities, giddiness, and buzzing of the head occurs, but these pass off on reducing the dose or stopping it for a few days. It may be given in capsules or as tablets.

Kurchicine is an **antiperiodic** and may be used by the mouth (2 to 5 grs.) with benefit in cases of dysentery complicated with fever.

Anthelmintics

BUTEA SEMINA. Syn.—Butea Seeds ; *Palas Bij*.

Source.—The seeds of *Butea frondosa*.

Composition.—Fat 18 p.c., albuminoid substances 19 p.c. and glucose. The fat exists in the form of *moodooga oil*.

Preparation

1. **Pulvis Buteae Seminum.**—The kernel dried and powdered, freed from the testa after soaking in water. *Dose.*—10 to 20 grs. or 0.6 to 1.2 grms.

Action and Uses.—The seeds are powerful **anthelmintics for round-worm** and may be used as a substitute for santonin, followed as usual by a dose of purgative.

ARTEMISIA, I. P. L. Syn.—*Kirmala*, Hind.

Source.—Artemisia consists of dried immature leaves or flowerheads of *Artemisia brevifolia* and *Artemisia maritima*, collected in early summer, or late spring when the flowerheads are approaching full development. Contains not less than 0.75 p.c. of santonin.

Dose.—15 to 25 grs. or 1 to 1.5 grms.

Action and Uses.—It is an anthelmintic for round-worm for which purpose it may be used in the form of powder at bed time to be followed by a purgative, preferably a saline in the following morning. It is however chiefly used as a source of santonin.

EMBELIA. Syn.—*Biranga*, Beng. *Baberang*, Hind. *Vidanga*, Sans.

Source. The dried fruit of *Embelia Ribes*, and of *Embelia robusta*.

Composition.—(1) *Embelic acid* or *embelin* 2.5 p.c. (2) An alkaloid *Christembine*, resin and a tannin.

Dose.—1 to 4 drs. or 4 to 16 grms. in powder.

Pharmacology and Therapeutics

These berries are considered as valuable **anthelmintics for tape-worm**, and may be used in powder or as infusion (without straining) early in the morning on an empty stomach to be followed by a simple purgative after 4 hours. The taste is not unpleasant.

VERNONIA. I. P. L. Syn.—*Somraj*, Beng. : *Vakuchi*, Sans.

It consists of fresh dried seeds of *Vernonia anthelmintica* with the glandular hairs intact.

Composition.—An alkaloid known as *vernonine*, resins and an oil.

Dose.—15 to 30 grs. or 1 to 2 grms.

Action and Uses.—Powdered seeds are used as anthelmintic both for round-worm (ascaris) and also for thread-worms (oxyuris). It may also be used as infusion.

Demulcents and Emollients

ISPAGHULA, I. P. L. Syn.—Spogel Seeds ; Psyllum Seeds ; *Isaphgul*, Beng.

Source.—The dried seeds of *Plantago ovata* and other species of Plantago.

Composition.—(1) *Mucilage*, 1 in 20 of water forms a thick tasteless jelly. (2) *Fixed oil* and albuminous matter.

Dose.—75 to 225 grs. or 5 to 15 grms.

Ispaghulae Testa. I. P. L. Syn.—*Ishabguler Bhusi*.—Ishabgul Husk consists of the dry seed coats of the seeds of *Plantago ovata*, obtained by crushing the seeds and separating the husks by winnowing.

Dose.—8 to 30 grs. or 0.5 to 2 grms.

Pharmacology and Therapeutics

Externally.—The bruised seeds, moistened with water, form an excellent, emollient poultice.

Internally.—Isaphgul is a **demulcent** and mild **laxative** acting like agar-agar by virtue of its bulk. Two to three teaspoonfuls of powdered seed taken at bed-time with a little sugar and water give one or two clear evacuations in the morning, without any griping. When soaked in water (1 in 40) it forms a mucilaginous mass which acts as a protective layer over the intestinal mucous membrane, and is used as a domestic remedy in **acute and chronic dysentery**. The mucilage also inhibits the growth of bacteria in the intestine and adsorbs toxins, thus preventing their absorption. It is often combined with powdered [illegible] seeds (see page 797) commonly known as

[illegible], the dose is 5 grs. every two or three hours, and this combination will be found to yield most encouraging results. The decoction is also used as demulcent in cough and sorethroat, and formed into a sherbet (seeds, sugar and water) it is used as a cooling beverage in gonorrhoea, when it acts as a mild diuretic and soothes the irritation of the urethra during urination.

OLEUM COCOIS, I. P. L. Syn.—*Narikel tel*, Beng. *Nariel ka tel*, Hind.—Coconut Oil is a fat obtained by expression from the kernels of coconut, the fruit of *Cocos nucifera* and *Cocos butyraceae*.

Characters.—Almost colourless or pale-yellow transparent liquid, solidifying at temperatures below 20°, below 15° it is a hard white pearl-white fat; fracture ...; odour reminiscent of coconut; taste, bland and agreeable. Soluble in 2 parts of alcohol (95 p.c.).

Composition.—Trimyristin and trilaurin, and smaller proportions of tripalmitin, tristearin and triolein; and the glycerides of the volatile caproic, caprylic and capric acids.

ACTION AND USES.—It is a bland unirritating oil and is largely used as a lubricant for hair dressing and for the manufacture of soap. It is also used as a basis for ointments and may be substituted for arachis oil. The oil prepared from fresh pulp is used as a substitute for cod-liver oil; only drawback is its indigestibility.

Cardiac Tonic

TERMINALIA ARJUNA. Syn.—Arjuna; *Arjun*, Beng.

ACTION AND USES

The bark possesses a reputation of being a valuable cardiac tonic and is extensively used in this country for all sorts of cardiac troubles and complications.

The reputation of the drug and the fact that it is extensively used and advertised as a cardiac tonic led us to make a careful investigation of its action on animals. Experiments made with liquid extracts obtained from reputed manufacturers and prepared in the laboratory show that it causes a fall of blood pressure in intact animals even in very small doses; while larger doses cause death of the animal from stoppage of the heart. On isolated hearts the beats are rendered weaker and eventually the heart stops from direct action on the cardiac muscle. These findings are directly opposite to the general belief. Further work is in progress to substantiate or controvert these observations.

Antiseptic

NEEM BARK. Syn.—Margosa Bark.

Source.—The dried bark of the stem of *Melia azadirachta*.

Composition.—(1) *A bitter amorphous resin.* (2) *Margosine*, a bitter alkaloid (3) *Margosic acid.*

PREPARATIONS

1. **Infusum Neem.**—1 in 100. *Dose.*—½ to 1 oz. or 15 to 30 mils.
2. **Tinctura Neem.**—1 in 10. *Dose.*—30 to 60 ms. or 2 to 4 mils.
3. Sodium and Potassium Margosates. Valuable in combating infections of diverse nature in any form of skin affections. Injections are said to be useful in *leprosy*.

Oleum Neem, I.P.L.—Neem Oil is expressed from the seeds of *Melia azadirachta*, collected late in summer and filtered.

Characters.—Deep yellow; odour disagreeable; taste, bitter and acrid.

PHARMACOLOGY AND THERAPEUTICS

Externally.—The leaves in the form of a decoction or poultice are largely employed to stimulate foul and indolent ulcers to a healthier action. The decoction is also used as an antiseptic lotion or general bath in many skin diseases. Weeping eczema quickly heals if a cold poultice of the bruised leaves is applied and allowed to remain till it drops off.

The oil is a valuable local **stimulant, antiseptic** and **bactericide.** Alone or in combination with chaulmoogra oil it is considered to be an effective application in **leprosy.** Injection of margosates and the local application of the acid have been found to be of value in the treatment of **leprosy** and **syphilitic** conditions.

Internally.—The bark is a **bitter tonic, astringent** and **antiperiodic,** the astringent properties residing in the outer layers. Before the introduction of quinine into this country, the bark, either in powder (1 dr.) or in concentrated decoction, was largely employed in **malaria.** Its decoction is used in many cases of malaria where quinine fails to effect a cure, or as a tonic during convalescence.

Sedatives and Hypnotics

RAUWOLFIA, I.P.L. Syn.—*Sarpagandha,* Sans; *Chandra* or *Chotachand,* Beng.

Source.—Rauwolfia consists of the dried root of *Rauwolfia serpentina* with the bark intact, collected in autumn from 3 to 4 year plants.

Composition.—Total alkaloids, 0.8 per cent. of dry powdered root, neutral resin, phytosterol, oleic acid, a mixture of unsaturated alcohols, a resinous acid, etc. Five crystalline alkaloids have so far been isolated and identified : (a) *Ajmaline* group consisting of (i) Ajmaline, (ii) Ajmalinine, and (iii) Ajmalicine ; (b) *Serpentine* group consisting of (iv) *Serpentine,* and (v) *Serpentinine.*

Dose.—15 to 30 grs. or 1 to 2 grms.

Preparations

1. **Extractum Rauwolfiae Liquidum, I. P. L.**—Prepared with alcohol (90 p. c.) to contain 1.0 p. c. of the total alkaloids. *Dose.*—3 to 6 ms. or 0.2 to 0.5 mil.
2. **Extractum Rauwolfiae Siccum, I. P. L.**—Contains 4 p. c. total alkaloids. *Dose.*—1/2 to 1 gr. or 0.03 to 0.06 grm.
3. **Tinctura Rauwolfiae, I. P. L.**—Liq. ext. 250 grms., alcohol (90 p. c.) q. s. 1000 mil. Contains 0.25 p. c. total alkaloids. *Dose.*—12 to 30 ms. or 0.8 to 2 mils.

Pharmacology and Therapeutics

The interest in the drug has recently been stimulated on account of its well-marked hypnotic and sedative properties and also of its blood pressure reducing property. No mention of these properties occurs in the ancient Indian medical literature, though the hypnotic action of the drug is known to the poorer classes as 'pagal-ka-dawa' or 'insanity cure herb.'

The pharmacology of the drug has been worked out at the Calcutta School of Tropical Medicine and the Department of Pharmacology, Carmichael (R. G. Kar) Medical College. The effects of the different alkaloids individually vary. Thus, ajmaline, serpentine and serpentinine have been shown to be stimulants of the central nervous system, serpentine being the more powerful and toxic of the three alkaloids. The **sedative** and **hypnotic** properties are present mainly in the alcoholic extract and in the total alkaloids free from ajmaline, serpentine and serpentinine. It is too early to ascribe definitely the sites of action of the various alkaloids or the factor or factors responsible for the hypotensive property of the whole drug. Some of the alkaloids have been shown to have definite depressant action on the vaso-motor centre, the heart and the blood vessels. The hypnotic effect may be due to a resin-fraction and not to the alkaloidal fractions, as was hitherto supposed.

The drug is extensively used for its sedative properties in mental conditions and in insanity. Crude alcoholic extracts are also being used to **reduce blood pressure** in hyperpiesis.

It is desirable that a *standardised* extract or powder is employed. Instances are on record where an intense bradycardia has been induced after uncontrolled medication with unauthenticated preparations. The drug is potent and effective and adequate precaution should be taken and cases chosen carefully for treatment. It sometimes fails to reduce the pressure possibly due to the preparation not being properly standardised or to bad selection of cases. While some patients show definite improvement others do not.

Haemostatic

AYAPANA, I.P.L. Syn.—*Ayapana*, Beng., Hind.

Source.—Ayapan consists of the dried leaves of *Eupatorium ayapana*. It yields not less than 0.1 p.c. of *ayapanin* and *ayapin*.

Composition.—(1) *Ayapin*, 6 : 7-methylenedioxy-coumarin. (2) *Ayapanin*, 7-methoxy coumarin. (3) Volatile oil.

Preparation

1. **Extractum Ayapanae Liquidum, I. P. L.**—Prepared with alcohol (60 p. c.) to contain not less than 0.1 p. c. of ayapanin. *Dose.*—30 to 90 ms. or 2 to 6 mils.

Action and Uses.—Both the active principles possess remarkable haemostatic property both when locally applied and also when used internally. They act by increasing the coagulability of the blood which occurs within half to one and half hours and lasts for over two and a half hours. Ayapan therefore is used as a haemostatic to check internal haemorrhage, e.g. haematuria, haemoptysis, etc. Since it acts when locally applied it may be used as an application wherever it can reach the bleeding surface. As an ointment it may be applied to bleeding piles.

Ecbolic

ASOKE. Syn.—*Asoka, Asoke*, Beng.

Source.—The bark of the tree, *Saraca Indica*.

Composition.—The bark contains a large amount of tannin and a colouring matter (haematoxylin) ; no active principle of the nature of alkaloid, essential oil, etc. was found. Mineral residue about 10 p. c.

Preparation

1. **Extractum Asoka Liquidum.**—Strength 1 in 1 with glycerin, alcohol and water. *Dose.*—30 to 60 ms. or 2 to 4 mils.

Action and Uses

The bark is largely used in indigenous medicine as an astringent and uterine sedative. It is also supposed to exert some stimulating effect on the endometrium and the ovary.

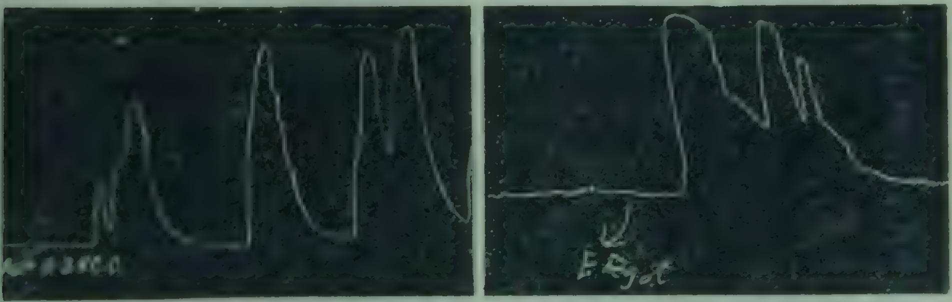


Fig. 39. Showing the effects of liquid Extracts of Asoke (left) and Ergot (right) on isolated gunea-pig's uterus suspended in oxygenated Ringer.

Asoke stimulates the uterus making the contractions more frequent and prolonged without producing tonic contractions like ergot or pituitary. It should therefore prove useful in all cases of **uterine haemorrhage** where ergot is indicated, viz., menorrhagia, metrorrhagia, postpartum haemorrhage, etc. Its effects are possibly produced through the sympathetic nervous system which is inhibitory to the intestine and generally motor to the uterus.

PART VII

PHARMACY AND DISPENSING

General Directions

1. **The dispensing room** must be well *lighted* and well *equipped*, with every necessary article, furniture and apparatus for compounding and dispensing purposes.

2. **Pure drugs of the best quality** are to be used, and preparations are to be made in strict accordance with the *official* and other *recognised methods*.

3. **Bottles are to be duly labelled.**—Those containing corrosive fluid must have *enamelled inscription*, or names engraved on glass. Bottles containing **poisonous** substances must bear an extra label—"**Poison**"—at their shoulders. It is a good plan to have also the *doses* printed on the labels.

4. **Poisonous drugs** must be kept within a separate glass case under lock and key.

5. **The counter and the apparatuses** for compounding and dispensing must be kept scrupulously clean, in good order, and ready for immediate use. Always clean and put away every article in its proper place after use.

6. **Testing of drugs** must be done occasionally so as to ensure their purity and strength. Substances like vegetable extracts, spirit of nitrous ether, hydrocyanic acid dilute, etc., require occasional looking after.

7. **Corks of good quality** should be used. Cracked, old, rotten and soiled corks should be rejected. The practice of pressing corks between the teeth should never be indulged in. Fit a cork before pouring the medicine into the bottle.

8. **Evidence of slovenliness** as regards externals does not encourage faith as to the care with which the contents have been dispensed.

9. **Prescription reading.**—Read through a prescription calmly and rapidly, without creating any suspicion in the mind of the presenter, but noting at the same time any inconsistency either in dosage or in combination.

10. **Consultation with the prescriber** must be arranged without delay, whenever possible, if there is any **poisonous** or **unusually large dose**, or a **grave incompatibility** in a prescription. The dispenser should on no account alter a prescription without the sanction of the prescriber.

11. **The directions** on the label should be written first of all before the medicine is dispensed. At the same time the prescription should be copied in the copy-book, noting afterwards, any peculiarity of compounding or dispensing. If the directions are in Latin, the dispenser should give their English translation. In India, the directions should be written in the familiar language of the place when the medicines dispensed are meant for those who cannot read English.

12. **Labels** should be neatly and distinctly printed without much flourish, and their margins carefully trimmed. "**Poison,**" "**shake the bottle,**" "**not to be taken**" and other accessory labels are best placed on the **shoulder** of a bottle. If affixed at the foot, the fingers holding the bottle may cover them, or a hurried patient may overlook them. The colour of labels for liniment and lotion ought to be different from that of mixture and powder. Orange-red and dark-yellow for the former and white for the latter may be used. Sometimes the labels for liniment and lotion are printed with red on white paper.

13. **Bottles for dispensing** mixtures should be of different shapes from those used for liniments and lotions. Amber-coloured or uranium bottles are best suited for silver nitrate lotions, and blue bottles for liniments. Bottles covered with blue paper can be used for silver lotions, when uranium or amber-coloured bottles are not available.

14. **The dispensing of two prescriptions simultaneously** should never be attempted. But if an infusion is to be made the dispenser ay set it on, noting on a bit of paper the time and the substance, nd placing it between the cover and the pot.

15. **The position of a prescription during dispensing** must be ch that the dispenser can read it while dispensing. This can be st accomplished either by fixing it to a hook on a counter-shelf, by holding it between the index and the middle fingers of the ft hand.

16. **Manipulation.**—Be expeditious in manipulation. Finish ing, sealing, labelling and wrapping as quickly as possible. The ding of powder envelopes between the lips, the handling of drugs, e stirring of mixtures with the fingers are to be avoided.

17. **The final reading of a prescription** is essential before the edicine leaves the hands of a dispenser, so as to make a revision his work.

18. **Graduation of bottles** must be accurate. Want of symetry of the bore makes a great deal of difference. Blown lines of aduation are generally wrong. Paper graduation is the best, but must be done by hand in each case. Mark-papers should either notched or lined equidistantly, but in either case the number of ses should be put down in figures on the label.

19. **Repetition of prescription.**—If a prescription contains such ugs as are likely to produce a cumulative effect, or a habit, or are toxic as strychnine, arsenic, lead, digitalis, opium, sulphonaides, etc., it should not be repeated unless sanctioned by the prescriber.

WEIGHING AND MEASURING

1. **Scale.**—An upright fixed beam and scale with a movable ass pan should be used. If a hand scale is used, hold it firmly by e left hand, never lift it too high above the counter, and judge the eight as much by the indicator as by the position of the scale. A licate scale should be used for weighing minute quantities of werful drugs; such as strychnine, hyoscine, arsenic, etc.

2. **Corroding substances.**—Substances which corrode or act on e brass should be weighed upon glass pans. Crystallised acids, line, bicarbonate of ammonia and similar salts should never be ighed on brass pans.

3. **Soft or sticky substances,** such as soft extracts, confections, ntments, etc., should be weighed on a piece of paper spread over right pan, after placing a corresponding piece of equal weight the left along with the weights. Scrape the medicine by a spatula om the paper after weighing.

4. **No guesswork** in weighing or measuring is allowed. Every ug must be either weighed or measured.

5. **Label upwards.**—In pouring out liquids, always keep the el of the bottle upwards in order that it may not be spoiled by e trickling down of the drops of liquid left on the lip of the bottle.

6. **Minim measure.**—From a few drops to a drachm, the liquid uld be measured in a minim glass. The true level of the surface the liquid in a minim glass is the midway between the highest st close to the glass and the lowest at the centre.

7. **Lip drops.**—The drops that hang from the lip of a bottle out which a liquid has been poured, should be caught upon the bottom the stopper, before putting it back into the mouth.

8. **How to drop.**—Before permitting drops to fall into any mixture the dispenser should allow a few drops to fall on a separate vessel till he is confident that he has a perfect control over dropping. If he is not sufficiently skilful, let him measure the drops into an empty glass until he is satisfied that he has obtained the correct number.

9. **Volatile liquids**, such as ether, chloroform, nitrite of amyl, dilute hydrocyanic acid, etc., should always be measured instead of dropped.

10. **The size of drops** varies considerably, and therefore when 'drop' is used, it should be measured by means of a tube which delivers in 20 drops 1 grm. of distilled water at 15°C.

11. **Division of a grain or a minim** is best accomplished by triturating or mixing the weighed or measured quantity with sugar of milk or any liquid excipient, and dividing the mixture as ordered. For instance, suppose that 24 pills are ordered, each containing 1/30 grain of strychnine hydrochloride. The total amount in the 24 pills will be $\frac{24}{30}$ =4/5 grain, therefore weigh out 1 grain of the salt and triturate it with 4 grains of milk sugar, making 5 grains in all. Then 4 grains of this mixture will contain 4/5 grain of strychnine hydrochloride. Take this amount and destroy the remainder.

WATERS

1. **Camphor water.**—2 ozs. of water dissolve only 1/12 gr. of camphor. The easiest way of making a good camphor water is to mix flowers of camphor with coarsely powder glass, tie the mixture in a muslin bag and suspend it by thread into the water from the cork. A good solution is obtained sooner by moving the bag up and down two or three times a day.

By dissolving 100 ms. of spirit of camphor in 40 ozs. of water, camphor water may be quickly obtained.

2. **Chloroform water** is made by the simple shaking of chloroform in water.

N. B.—For the preparation of **aromatic waters,** *see* page 17.

DECOCTIONS

1. **Drugs** should be coarsely powdered or sliced before they are boiled in water for 5 minutes or longer. If the comminution is too fine some sediment deposits. The drugs should always be put in cold water before boiling.

2. **Decoction pots** should be enamelled or tinned and covered. A false bottom made of tinned or silver gilded copper wire half an inch or more above the bottom should be used to prevent imparting a fusty odour to the decoction from the particles of the drugs adhering to the bottom of the vessel during boiling.

INFUSIONS

1. **Drugs for infusion** should not be too finely comminuted.

2. **No other water than distilled water,** boiling or cold, is to be used.

3. **Suspension of drugs is essential.** A muslin bag containing the drug can be suspended by a thread from the lid of a covered pot, or a Squire's or Maw's infusion pot may be used.

4. **Uniform temperature,** as far as possible, should be maintained.

5. **Hard spring water** does not give a good colour, as the extractive matters are not well dissolved by it.

6. **Infusions** should be made **fresh** and these are now named in the Pharmacopoeia as **fresh infusions** as distinguished from concentrated infusions which after dilution resemble the fresh infusions

EMULSIONS AND MIXTURES

Emulsion is a mixture of two liquids which though insoluble in each other, the insoluble substance remains finely divided or broken up in the form of globules, which do not coalesce again to form separate miscible fluid, by the presence of a third substance, known as the *emulsifier* or *emulgent*. Emulsion resembles milk owing to the suspension of resinous or oily bodies in water. Thus, castor oil and water are not miscible and when shaken together the oil will be broken up in small globules and will temporarily disperse in the water to separate again on standing unless an emulsifier is used. In this the oil is dispersed in water, forming what is known as *oil-in-water* emulsion. In another form of emulsion, the water is dispersed in oil, forming *water-in-oil* emulsion. This type of emulsion is produced by wool fat, emulsifying wax, bees wax, etc.

Emulsions are prescribed (*a*) to help administration of oily substances which will not mix with water ; (*b*) to help easy absorption of the oily substance which is presented in a finely divided and dispersed state in some vehicle ; and (*c*) to make it more palatable.

1. **The first fundamental rule** *in the compounding of a mixture is to avoid chemical decomposition taking place among its ingredients, unless such is the implied intention or the express order of the prescriber.*

2. **Distilled water** should be used in compounding. Tap or other waters produce a considerable change in mixtures owing to the presence of traces of calcium and magnesium salts. For example, Tinct. Cardam. Co. produces a brilliant crimson colour with tap, and a reddish-brown with distilled water. Tinct. Lavand. Co. gives a bright mixture with distilled and a muddy one with tap water. Ordinarily the word "aqua" means tap water. If the prescriber wants distilled water to be used he should write "aqua destillata."

3. **Order of mixing.**—It is not the spirit of practical pharmacy to mix the ingredients in the order in which they are written in a prescription. The dispenser should exercise his own judgment in determining the best method of effecting a combination.

It is a good plan first to pour in the tinctures and spirituous fluids as they are measured, next add syrups and essences, and lastly fill up the bottle with the vehicle.

4. **Poisonous drugs** such as arsenic, strychnine, perchloride of mercury, hydrocyanic acid dilute, etc., should be separately dissolved and then added to the mixture last of all, immediately before corking the bottle. In this way you avoid the possibility of putting them in twice over.

5. **Mortar and pestle** should never be used if the ingredients are easily soluble. Dispense syrups and fluid preparations in such an order that the vehicle will finally rinse out the measure glass.

6. **Shaking.**—All mixtures should be briskly shaken before labelling, to ensure a thorough incorporation of the ingredients.

7. **Heat** should not be used to help the solution of salts when they will not entirely dissolve in cold water, for they are sure to crystallise on cooling. Suspension is the best method under such circumstances.

8. **Wholly or partially soluble vegetable drugs**, especially which contain tannin, should be *mixed with earthy and metallic salts in largely diluted solutions.*

9. **Gelatinous mixtures.**—Some mixtures become *gelatinous* on keeping, due to the growth of an organism called *viscous ferment.* An addition of 20 per cent. of alcohol to the mixture prevents this.

10. **Chemical reaction.**—If there is a chance of chemical reaction taking place, the ingredients which are likely to act with one another, should be freely and separately diluted or suspended, before

mixing. The mucilage of acacia always suspends the precipitate uniformly, and to some extent retards or modifies the chemical decomposition.

11. **Froth.**—Sometimes a lot of froth rises as the result of shaking especially if the mixture contains vegetable solutions thus preventing the bottle from being filled or corked. A few drops of alcohol remove this.

12. **Insoluble powders** are sometimes prescribed in a mixture. These fall into two groups : *diffusible* and *indiffusible*. Powders such as rhubarb, chalk, compound powder of jalap, heavy and light magnesium oxide and carbonate, quinine sulphate are diffusible and should be triturated with a small quantity of water in a mortar to produce a thin paste, before mixing with the vehicle. No suspending agent should be used by the dispenser unless it is found that equal dosage of the substance is not possible without one. Most of the insoluble powders are easily diffusible and do not require a suspending agent. In any case "shake the bottle" label should be used.

A substance is regarded as *indiffusible* when it will not remain evenly distributed in the vehicle for a long period to ensure uniformity of the dose. They are : acetanilide, acetylsalicylic acid, barbitone, benzoic acid, betanaphthol, bismuth salicylate and oxychloride, chlorbutol, resinous substances, quinine salicylate, quinidine sulphate, salicylic acid, etc. These require a suspending agent.

13. **Medicinal filtrates** produced in a mixture should not be filtered, but suspended. But if any foreign particles float on a clear solution, they should be removed either by straining or by filtration through wetted cotton or tow plugged lightly into the neck of a funnel. All mixtures depositing a sediment should bear the label *"shake the bottle."*

14. **Mucilage** should be recently prepared, but it can be kept ready made for some time provided that the bottle containing it is full up to the neck and properly sealed.

15. **Oils** are best emulsified either by rubbing them up with gum or by mixing them with an alkali, or with both. Copaiba is well emulsified with gum and alkali. Essential oils are best emulsified with tragacanth powder in the proportion of 10 grs. for every ounce, or yolk of egg.

16. **Scale preparations** in a mixture are either to be dissolved in a mortar with warm water or poured into the bottle with the vehicle and shaken briskly. If poured in a dry condition into the bottle, and the water or vehicle added afterwards, a sticky mass cakes at the bottom.

17. **Volatile ingredients in a mixture.**—Volatile drugs such as ammonia, ether, chloroform, hydrocyanic acid, etc., should never be mixed with hot fluids, and should always be added last of all, after the vehicle has been poured into the bottle. Care should be taken that sufficient space is left for the requisite quantity of the soluble ingredient. As soon as this has been added, the bottle must be tightly corked and well shaken.

18. **Resinous substances** should first be finely powdered and triturated with mucilage of tragacanth and finally the vehicle is added. They may also be dissolved in alcohol and dispensed in the same way as resinous tinctures.

SUSPENDING AND EMULSIFYING AGENTS

Suspending agents are often necessary to keep insoluble substances in a state of suspension so that each dose should contain a reasonably correct proportion of the compound. Suspending agents are also necessary when liquid preparations containing resinous substances are used in a mixture, as these may form precipitate and adhere to the side of the bottle. If the prescriber dose not

order any such agent the dispenser should use his own judgment in deciding whether any suspending agent should be used. The following substances are commonly used as suspending agents, *viz.*—Acacia, tragacanth, or mucilage of acacia or mucilage of tragacanth, glucose, or syrup. The best suspending agents are—Pulv. Trag. Co., **Mucilage of Tragacanth.**

Mucilage of acacia should be used in the proportion of 1 dr. for each fluid ounce of the mixture. It however has the disadvantage of making mixtures sometimes lumpy, as for instance with bismuth salts, when tragacanth is more preferable and should be used in the same proportion.

There are many *emulsifying agents* and they are almost invariably colloidal substances and thus remain in a state of extreme subdivision in which state its surface area is enormously increased. This state of subdivision demands expenditure of energy, and this energy becomes stored up on the surface of the particles as surface energy, and more finely divided the substance, the greater is the surface area and, consequently, greater its surface energy with greater power to adsorb other substances to its surface.

The emulsifying agents are :—

Acacia powder.—The formation of a good emulsion depends upon the right proportion of oil, water and gum. The usual rule is to use one part of powdered gum acacia for every four parts of fixed oil. For volatile oils the proportion is half the quantity of gum as oil. For making emulsion with substances containing oleoresins like copaiba or male fern the proportion should be equal quantity of each.

Powdered gum tragacanth is inferior to acacia, as the oil globules are larger than acacia emulsion and therefore the emulsion with tragacanth is not so white. Gum tragacanth is used more for emulsifying volatile oils and less for fixed oils. The proportion being 10 grs. of the gum for every ounce of the oil. It is often used along with acacia to increase viscosity of the emulsion.

Cera Emulsificans, Emulsifying Wax or **Lanette Wax SX** is used as an emulsifying agent in the preparation of creams, ointments and other emulsions.

Yolk of egg is largely used for emulsifying cod-liver oil. Its emulsifying power is twice that of powder acacia. 4 drs. will emulsify 4 ozs. of fixed oil and 2 ozs. of volatile oil. It has the advantage over gum emulsion in that it does not separate on the addition of acids, salts, glycerin or syrup. If however the egg-emulsion is kept for long it undergoes putrefaction and imparts a bad odour to the emulsion. Sometimes a little benzoic acid or 5 p.c. alcohol is added as a preservative.

Alkalies.—The hydroxides of potassium, calcium, ammonium and sodium are generally used. They form soaps by combining with the fatty acids contained in most of the fixed oils of vegetable origin. Volatile oils which do not contain any fatty acid cannot be emulsified with alkalies. Lime water and ammonia are however not used for emulsions intended for internal use. They are largely used for liniments and substances meant for external application.

Soaps.—These are best emulsifying agents for lotions, liniments and other preparations for external use.

Saponins.—These occur in certain vegetable substances and form froth when shaken with water, similar in appearance to the froth produced when soap is shaken with water. The drugs which contain most saponins are quillaia and senega and the most convenient sources of these saponins for dispensing purposes are the tinctures of the respective drugs. Since both these substances have a therapeutic action of their own they should not be used for making emulsions for internal use unless especially ordered.

Casein and **mucilage of starch** are also used as emulsifying agents

MIXTURES AND EMULSIONS OF SPECIAL DRUGS

1. **Acacia** in a mixture is best added in the form of mucilage, which should be freshly made.

2. **Almond oil** does not emulsify well with mucilage or powdered gum, but a small quantity of liquor potassae or carbonate of potassium without mucilage answers well.

3. **Ammoniacum, Myrrh** and **Guaiacum** should be triturated first with a little water or some similar vehicle so as to form a thin paste. These do not require a suspending agent as the gum present in these is sufficient to suspend the resin. The resulting mixture may be strained through muslin.

4. **Ammonium Bicarbonate** should be dissolved in a cold vehicle, only translucent pieces being used. Those portions which have effervesced are wanting in strength.

5. **Benzoic acid** should be powdered before mixing. If there is a tincture in the formula it should be dissolved in it, and water added gradually with shaking.

6. **Bismuth Carbonate and Subnitrate** are often prescribed in a mixture without any suspending agent. They should first be triturated in a mortar with some of the vehicle to form a paste and then the water should be added to adjust the volume. They are easily diffusible and do not ordinarily require any suspending agent. If any suspending agent is used, acacia should be avoided for reasons explained on page 807. Bismuth subnitrate is chemically incompatible with potassium or sodium bicarbonate, producing a large quantity of carbonic acid gas when mixed in a mixture. The gas must be allowed to escape by gentle heat before bottling, otherwise the bottle may subsequently burst or the cork be suddenly blown out. An equivalent quantity of bismuth carbonate may be substituted as the finished mixture contains the same. Bismuth salts and iodides produce bismuth oxyiodide which gives a brownish-red colour to the mixture though therapeutically it is harmless.

7. **Borax** powdered and rubbed up with mucilage makes a soft, jelly-like mass. But a limpid mixture may be obtained by mixing freely diluted mucilage with a solution of borax in warm water.

8. **Butyl-chloral Hydrate** forms oily compounds with alcohol, insoluble in water. Dissolve in glycerin and warm water. **Chloral hydrate** behaves in the same way, and is decomposed by alkalies, liberating chloroform.

9. **Caffeine Citrate** forms a syrupy liquid when mixed with three times its weight of water ; on addition of more water, caffeine hydrate is precipitated. This is again redissolved on further dilution.

10. **Camphor** in a mixture is treated with three times its weight of alcohol, in the same way as resinous tinctures, *i. e.* dissolve it in alcohol first and then treat as a tincture. Acacia is a better suspending agent.

11. **Chlorate of Potassium and Hydrochloric Acid.**—Sometimes a prescription containing potassium chlorate, hydrochloric acid, and water comes to the dispenser for dispensing. Here the object is to make a solution of chlorine, and is best done by adding the acid directly to the salt, corking the bottle for a while before adding water, so as to make a solution of chlorine in water.

Chlorate of potassium with syrup of iodide of iron liberates *free iodine* which has proved fatal.

12. **Cod-liver Oil** is well emulsified by the following method. Place powdered tragacanth in a dry mortar and triturate a little of the oil, then add the yolk of an egg and the oil and stir briskly, adding water as the mixture thickens, and lastly mix flavouring oils and water alternately, with constant stirring, avoiding frothing. The mixing of lime water 1 to 5 with cod-liver oil greatly facilitates its

emulsification, and reduces its tendency to cause eructations. Lime water and acacia gum emulsify cod-liver oil just as yolk of egg.

13. **Copaiba Balsam** can be well emulsified by rubbing it with about its own weight of powdered gum acacia and liq. potassae. The resin acids combine with caustic potash and form a soap-like substance which helps emulsification.

14. **Ether** should never be mixed with hot liquids, and must be added last to a mixture.

15. **Ferri Sulphas** soon gives a rusty colour to a solution from the production of ferric hydroxide, which is retarded by adding an acid.

16. **Glycerin** is used as a sweetening agent for mixture, especially those that contain perchloride of iron.

17. **Iodine** is very sparingly soluble in water, but iodide of potassium helps solution to the extent of three-quarters of its own weight. Salts of ammonia also increase its solubility by the formation of a soluble salt, ammonium iodide. Some essential oils such as oils of peppermint and fennel, chemically combine with iodine. Strong solution of iodine with solution of ammonia, or with ammoniated camphor liniment, precipitates iodide of nitrogen, which is a most dangerous explosive (*see* Explosive Combinations, page 65).

18. **Morphine salts** should not be dissolved by heat, for at a temperature above 104°F. their solutions turn yellow or brown.

19. **Paraldehyde** is soluble in water in the proportion of 1 in 9. If it is present in a mixture in excess of its solubility it should be emulsified with tragacanth powder.

20. **Phenacetin** in a mixture requires careful treatment. It should be first finely powdered and then mixed with pulv. trag. co. in the proportion of 2 to 5 grs. for every ounce of the mixture, and then the vehicle added with trituration in a mortar. The same procedure should be followed for acetanilide.

21. **Phenazone** is sometimes a troublesome drug to deal with in a mixture. It is rather a free base, and gives precipitate with tannin, alkaloids and many other substances. Thus, with alkaline salicylates it forms *salipyrin* (insoluble); with ferric chloride, *ferripyrin* (orange red); with free iodine, *iodopyrin* (insoluble); with chloral hydrate, *hypnal* (insoluble), etc.

22. **Potassium Iodide** is decomposed by acids, liberating *free iodine*, which may produce fatal results. This also happens when potassium iodide is mixed with solution of perchloride of iron.

23. **Quinine salts.**—The following points in respect of the mixing of quinine salts should be noted :—

(*a*) It produces an *insoluble salt* when added to a strong mineral acid; the acid should be freely diluted with the vehicle before the alkaloidal salt is mixed.

(*b*) When it is prescribed with spirit of nitrous ether, tincture, ether, or any spirituous liquids along with glycerin or syrups and water, the quinine is to be first dissolved in the undiluted spirituous mixture and then glycerin or syrup added, and lastly the vehicle is gradually mixed. If no mucilage is ordered it may be added to prevent quinine from adhering to the sides of the bottle.

(*c*) When ordered with bark or any other substances containing tannic acid, it deposits a precipitate of tannate of quinine which should not be filtered.

(*d*) No acid should be added by the dispenser to make a solution if it is not prescribed. The quinine is then to be rubbed up in a mortar with little mucilage and diffused in water, or added to the vehicle in its crystalline state with "shake the bottle" as a direction. The former is the better method.

(*e*) Quinine salts are *incompatible with alkalies*, such as bicarbonates, carbonates, hydrates, sp. ammon. aromat., etc. They

should be suspended and diluted *separately* before mixing; a small quantity of mucilage will make a better mixture.

(*f*) Ammoniated solution of quinine gives a precipitate when diluted with water, but the addition of a little mucilage (1/2 dr. to 1 oz. of mixture) suspends it.

(*g*) Mercuric chloride throws down a poisonous precipitate which can be dissolved by diluted hydrochloric acid. Glycerin and gum also retard to some extent chemical reaction.

(*h*) When it is ordered with salicylates in a mixture, an ugly looking mass, salicylate of quinine, forms inside the bottle which refuses to flow out. The mixture may be improved by rubbing mucilage with quinine and gradually mixing the salicylate dissolved in a large quantity of water, and agitating very briskly.

(*i*) Neutral solution of quinine and iodide of potassium do not react chemically, unless there is an acid present, free or liberated, in which case iodine is set free.

24. **Spirit of Nitrous Ether** turns *acid* due to the fact that the ethyl nitrite becomes hydrolised on keeping with formation of free nitrous acid and should therefore be made *alkaline* before being mixed with iodides or bromides otherwise free iodine or bromine will be liberated and will darken the mixture. It can be kept permanently alkaline or neutral by dropping a few crystals of potassium bicarbonate in it.

25. **Strychnine** in a mixture containing alkalies is precipitated to the bottom of the bottle, and fatal results may follow the swallowing of the last dose. Bromide and iodide of potassium, also liq. hydrargyri perchloridi throw down insoluble precipitates of strychnine compounds.

26. **Tannic acid** should be dissolved in pure distilled water, as tap water makes the solution opalescent. It precipitates alkaloids in solution and gives with iron an inky colour. Alkalies give precipitates, and turn the mixture brown to black. Mucilage makes it flaky.

27. **Vegetables extracts** should be carefully *rubbed* in a warm mortar with a little water till a soft paste is obtained, with which the vehicle is to be gradually mixed. If they are resinous rub them with two or three times their weight of powdered acacia in warm water, and then gradually mix with the vehicle when cold. *Ext. Filicis* may be triturated with its own weight of powdered acacia and water added gradually with constant stirring.

PILLS

1. **In making a pill-mass,** the following points should be observed :—

(*a*) Put the substance (powdered) prescribed in smallest quantity into the mortar first and triturate it with the next smallest (if it is powder), add the next, again triturate, and so on.

(*b*) Toxic substances (*e.g.* alkaloids and arsenic) should always be triturated well with double their weight of hard powder (*e.g.* lactose), if there is none in the pill constituents, before adding the other ingredients gradually.

(*c*) Potent extracts which are prescribed in the pill should not be treated as excipients, *e.g.* Ext. Nucis Vom. gr. 1/8 with Pulv. Aloes gr. 2 and Pulv. Ipecac. gr. 1/2. Here rub the extract with the ipecacuanha, add a little of the aloes, again triturate, and continue thus until the extract is equally divided throughout the whole.

(*d*) Essential oils should be treated like No. (*c*). Thus in the case of Pil. Aloes, the oil of caraway should be triturated lightly with the powdered soap (the oil being added gradually); then aloes, trituration, aloes, trituration, etc.*

* Chemists and Druggists Diary, 1898.

2. **Pills under one grain** should be made up to 1 grain by the addition of liquorice powder or sugar of milk. Fractions of a grain of such **powerful drugs** as strychnine, perchloride of mercury, arsenic, etc., should be intimately triturated with sugar of milk, and then made into pill-mass with suitable excipients.

3. **Pills liable to crumble** will keep their shape for a reasonable time if some fibrous materials, such as liquorice powder, or lycopodium are added to the mass. If the pill-mass is too soft it should be hardened on a hot plate, but if the ingredients are hard and brittle, they should be massed in a warm mortar. When the pill-mass contains dry vegetable powders some minutes must be allowed for the absorption of moisture before rolling.

4. **The same spatula** should never be dipped into the extract pot after it has been used to scrape the pill-mass from the tile, pestle and mortar.

5. **To prevent sticking together**, cinnamon or liquorice powder, mixture of starches, powdered French chalk are used. Pills containing hygroscopic and volatile ingredients should be varnished or coated and then dispensed in a well-stoppered or corked bottle. Pills for silvering should never contain glycerin.

6. **Substances that are decomposed by iron,** such as silver nitrate, copper, and bismuth salts, corrosive sublimate, and calomel, should not be mixed in an iron mortar, or scraped by an iron spatula.

7. **Crystalline salts** soluble in water should be very finely powdered, and massed with glycerin of tragacanth and some inert powder. Before silvering, they must be varnished with tolu and dried. Glycerin of tragacanth is the best excipient for insoluble salts.

8. **Essential oils.**—Soap and sometimes soap and powdered liquorice root make a good excipient. Wax is to be avoided. When there is much essential oil, the addition of liquor potassae helps greatly.

EXCIPIENTS

An excipient is a substance, either solid or liquid, added to bind the ingredients of a pill-mass into a plastic and adhesive mass. If none of the ingredients in the pill are suitable for producing a pill-mass, then it is necessary to add an excipient. The selection of a suitable excipient in these circumstances is done by the dispenser, which however requires experience. The following excipients are commonly used:—

1. **Acacia** in powder is a good excipient when judiciously used. It however makes the pill hard. With calomel it makes a regular cement. Combined with equal quantity of tragacanth it is better than acacia alone, and is known as Pulvis Acaciae Co. It is frequently combined with syrup of glucose. It should not be used with wax, fats or oils, or with creosote.

2. **Alcohol** softens resinous substances, but the mass should be quickly rolled, otherwise it will crumble.

3. **Calcium Phosphate** in minute quantities gives a pilular consistence to greasy substances and essential oils when soap is not admissible. It is a good desiccant.

4. **Castor oil**, with or without soap, is a good excipient for making camphor pills.

5. **Extract of gentian** though commonly used is not particularly adhesive and is dark in colour.

6. **Glycerin** keeps pills soft, but it is very hygroscopic. The addition of one-third of its weight of water overcomes its hygroscopic property. It is useful for pills liable to become hard.

7. **Glycerin, mucilage of acacia, water** and **alcohol** in equal parts makes a good general excipient.

8. **Syrup of liquid glucose** contains liquid glucose 1, syrup 2, and is a serviceable excipient.

9. **Kaolin ointment** is useful for massing oxidisable and reducible ingredients ; but has no advantage over lanolin with which it may be combined.

10. **Lanolin** may be used in massing certain scale preparations. Being non-oxidisable it may be used to mass potassium permanganate or silver nitrate with prepared kaolin.

11. **Liquorice or marshmallow** in powder are absorbent and give elasticity to the soft mass. They are useful for pills containing oils or phenol.

12. **Soap powder** is the best excipient for vegetable powders, extracts and gum resins. It neither hardens nor crumbles. It should not be used for masses containing acids, acid salts, metallic salts, and substances containing tannin.

13. **Tragacanth** powder gives in small quantities solidity and elasticity to a soft mass ; more so when the compound powder is used.

14. Wax is not much used now for it makes pills indigestible though it makes a beautiful pill-mass with camphor, creosote, phenol, and most of the essential oils.

ROLLING, CUTTING AND ROUNDING OF PILLS

Having prepared the pill-mass to proper consistency it should be rolled out on a pill tile with a spatula to the required length for the number of pills ordered by bringing it along side of the scale in the tile. Before cutting the mass into pills, it is a good plan to weigh the whole mass to see that it corresponds to the total weight of the ingredients, a precaution against careless weighing. When a large number of pills are to be prepared the rolling is done in a pill cutting machine (*see* fig. 40) by putting the mass or cylinder on the rolling board and rolling it with the under surface of the cutter by moving it with two hands backwards and forwards. It is important that the pill pipe should be uniform in thickness and perfectly

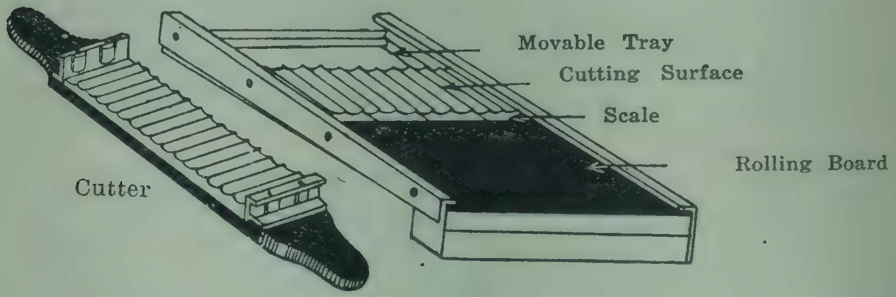


Fig. 40.—Pill Machine

cylindrical, care being taken that the ends do not taper out thin. The pill pipe when ready should be brought along side the scale on the machine to see that it fits the number of divisions corresponding to the number of pills into which it has to be divided. The dispenser being satisfied brings the pill pipe with his finger on to the grooved part of the machine. The cutter with the grooved surface downwards is pressed on the pill mass with both hands, and with a few jerking movements the pills are cut through and pushed into the removable tray. It is better to put some inert powder (liquorice root or French chalk) to prevent adhesion of the pills. If the pill-mass is properly prepared and the operation successful no further treatment is necessary ; but the track of the machine will be visible

on the pills and therefore these require finishing to make them perfectly globular. This is done by placing the pills on a dusted slab and rolled with a pill rounder or finisher. These are shallow, circular, boxwood trays not deeper than the pills which one wants to roll.

PILLS OF SPECIAL DRUGS

1. **Aloes** is best made into pills with syrup of liquid glucose. **Aloin** is massed with glycerin of tragacanth.

2. **Antipyrin** makes a good pill with glycerin of tragacanth.

3. **Argenti Nitras and Argenti Oxidum.**—The nitrate decomposes in the presence of organic substances and should be rubbed to a fine powder with twice its weight of kaolin and massed with lanolin. The oxide parts with oxygen readily with creosote, ext. gentian, etc. It should be massed with kaolin ointment.

4. **Bismuth** salts are best made into pills with glycerin of tragacanth.

5. **Butyl-chloral Hydrate** makes a good pill-mass with equal parts of powdered acacia, tragacanth and syrup, or glycerin of tragacanth.

6. **Calcium Sulphide** should be triturated with lactose to increase its weight if necessary, and massed with powder acacia, tragacanth and glycerin. Syrup of liquid glucose being slightly acid in reaction may liberate H_2S. The pills should be varnished to protect from decomposition from the air.

7. **Camphor** should be powdered first with a few drops of alcohol and after the evaporation of the spirit, use powdered hard soap and mass with syrup of liquid glucose.

8. **Camphor Monobromata** should be triturated with Pulv. Trag. Co. and massed with a little glycerin and water.

9. **Carbromalum** is made into a pill with glycerin of tragacanth.

10. **Cinchophen** makes a pill with compound acacia powder, 2 p. c. of tartaric acid and syrup of liquid glucose, or may be made with soap and glycerin of tragacanth.

11. **Chlorbutol** with acacia and syrup of liquid glucose.

12. **Citrate of Iron and Quinine** can be made into a pill by the addition of rectified spirit and rolling the mass quickly, or use kaolin and lanolin.

13. **Codeine** can be massed with half its weight of powdered liquorice and glycerin of tragacanth.

14. **Creosote** with powdered curd soap gr. 1 and powdered liquorice gr. 2 for each minim makes a good mass. **Guaiacol** should be treated like creosote.

15. **Emetine and Bismuth Iodide** pill is made with acacia and tragacanth. The pills should be keratin coated or salol varnished.

16. **Ferri Sulphas.**—The granular sulphate forms a good pill with glycerin of tragacanth and a little powdered sugar of milk. When 5 gr. are used for each pill, it is better to use the dried salt of which 3 gr. equals 5 gr. of the undried salt. Liquid glucose makes excellent excipient for dried salt.

17. **Gallic Acid and Tannic Acid** make good pill-mass with glycerin of tragacanth.

18. **Hydrargyrum c. Creta** can be massed with glycerin of tragacanth. It should not be vigorously triturated in a mortar, as the mercury may separate.

19. **Hydrargyri Perchloridum** should be finely triturated with lactose and made into a pill with compound powder of acacia and syrup of liquid glucose. Calomel pills are also made in the same way.

20. **Menthol, Thymol, Camphor,** etc., or substances which become oily should be mixed with half the quantity of powdered curd

soap and 1/4 the quantity of beeswax and then massed with powdered liquorice root.

21. **Phenol** is first mixed with 2 grs. of liquorice for each grain, then triturated vigorously and rolled into pill quickly. A drop of mucilage of acacia may be necessary.

Pills containing phosphorus require varnishing or a pearl coating.

22. **Potassium Permanganate** requires careful treatment, for it soon oxidises organic matter, such as sugar, syrup, vegetable extracts, etc., when brought in contact with it. It can be made into a good pill-mass by mixing it with kaolin 50 p.c. and then making the pill-mass with lanolin. Work the mass gently. Vigorous rubbing or the introduction of even a trace of foreign matter may set up combustion.

23. **Quinine Sulphate** with tartaric or citric acid make an excellent mass. Sometimes a drop or two of glycerin or water may be necessary in dry weather. The pills must be varnished or capsuled, otherwise, they will become soft and sticky by damp. Glycerin of tragacanth is also a good excipient.

24. **Zinc Valerianate** makes a good mass with a little powdered acacia and spirit. Glycerin of tragacanth and liquorice powder may answer well.

PILL-COATING

Coating of pills is necessary to make them look more elegant, to disguise their unpleasant taste, to protect them from decomposition by contact with the air, and sometimes to prevent their action in the stomach.

The general rule in coating of pills is that *all pills requiring a coating should be perfectly made, of a firm consistence, and free from contamination and powder.*

Silvering is done in a covered earthenware pot or a boxwood pill-silverer (Fig. 41). The pills being damped with thin mucilage are dropped on to a silver leaf put within the silverer. The cover is then put on and the silverer is shaken for about a minute. After the superfluous fragments of silver-leaf have been blown off, the pills are exposed to air for a few minutes to dry. One silver leaf covers six 5-gr. pills. When the pills are too damp more leaf is required, moreover the finish is not so elegant. A better and finer silver can be obtained by putting the pills and leaf in a covered porcelain pot or a metallic silverer, heating the pot or silverer over a spirit lamp and rotating it as before.

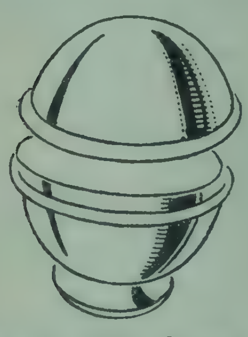


Fig. 41.—Pill Coater or Pill silverer.

Pills containing asafetida, mercury and sulphides should not be silvered unless they are very *stiff* and *varnished* otherwise the silvering will soon get blackened.

Gelatin-coating.—A coating solution is made by dissolving 1 of gelatin in 4 of water in a water-bath, straining while hot, and cooling it afterwards. If there are air bubbles the solution should be reheated. The pills are now stuck on the points of pins or needles and dipped into the warm solution. The pills are taken out slowly and rotated for a few seconds and then stuck into a sheet of cork or pincushion by their opposite ends. As soon as the outside coating dries, the needles are withdrawn and the holes close of themselves.

Sugar-coating is rather a complicated process. The following is the most practical method :—Pills well dried on the surface are placed in a tinned copper bowl with a flat bottom, or an enamelled iron

dish, the surface of which has been moistened with syrup, or syrup and gum. They are then rotated and gently heated, very finely powdered sugar 7 parts and starch 1 part being dusted on, and the motion kept up till a perfectly dry, hard and whitish coating is obtained, the operation being repeated if necessary.

Pearl coating.—It is done in the same way as sugar coating with the exception that fine white French chalk is used in place of sugar and starch. This coating sometimes becomes too thick so that the gastric secretion fails to penetrate it. For a perfect coating the pills must be dry. If they contain any hygroscopic substances, they should be varnished before coating.

Keratin-coating.—Keratin solution is made by first removing from horn shavings all that is soluble in pepsin and diluted hydrochloric acid, dissolving the residue in alcoholic solution of ammonia or acetic acid, and then evaporating the solution to the consistence of a liquid gum. The pills are simply rotated with the solution in a pot and dried on a slab. The coating often gets sticky. Pepsinised keratin can be bought and dissolved in any of the above solvents. Drugs intended to pass undissolved through the stomach are coated with keratin or salol ; as emetine-bismuth-iodide.

Varnishing.—The solution used is sandrac 1, alcohol 2, and ether 2. Smear an ointment pot or a porcelain slab with some oil, *e.g.* olive oil or almond oil. Pills for varnishing should be highly polished and free from any powder. Put the varnish in the proportion of 1 drop for each pill in a flat covered pot, cover and rotate for a few seconds say for 15 seconds. Transfer the pills into the oiled porcelain slab or the developing dish and turn each pill over and leave them to dry.

Salol-varnishing.—The varnish contains salol 2, shellac 3, absolute alcohol and ether of each 3, which should be applied several times till a thick coating is obtained. Or salol can be melted by heat in a copper bowl and the pills rotated as in sugar-coating.

Enteric-coatings are employed when pills are intended to pass through the stomach unchanged so that they can act in the intestine. The gelatin-coated pills are dipped in formaldehyde solution B.P., and dried. Many so-called enteric-coated pills are useless. These coatings are known as "glutoid" coating.

POWDERS

1. **Compound powders.**—The B.P. gives no direction as to the manner of mixing compound powders, consequently the dispenser is left to his own experience and resources in compounding them. The following hints, however, will greatly help him.

(*a*) **Powders must be thoroughly mixed** in a mortar or on paper. Powders mixed by a spatula on paper and sifted are more diffusible in water than those rubbed up in a mortar. Powders for insufflation should only be loosely mixed on paper.

(*b*) They should be **passed and repassed through a fine hair sieve** as often as possible. By repeated sifting and shaking in a bottle the ingredients are thoroughly incorporated and a uniformity **of colour is obtained.**

(*c*) They should be **very lightly rubbed** in a mortar if this process is at all adopted, otherwise they would cake.

(*d*) **Ingredients in smaller quantities** should first be thoroughly mixed together, and afterwards large quantities be gradually incorporated.

2. **Folding Paper and Boxes.**—Powders should be folded in ordinary writing paper, or better if possible, in demy glazed powder-paper made for the purpose. Waxed or paraffined paper is to be used for hygroscopic drugs. Coloured paper is used for powders for lotions. Folded powders should be of the same breadth and length,

better done on a powder-folder. Powders under six are generally dispensed in a small oblong envelope on which the words "The Powder" is printed ; but those over six in a cardboard box or bottle with a label gummed outside.

3. **Waxed Paper and Tinfoil.**—Drugs that are **perishable**, as ergot ; that are volatile, as camphor, chlorbutol ; that are **hygroscopic**, as potassium acetate, carbonate and citrate, sodium iodide, etc. ; that are liable to **decomposition**, as calcium sulphide, valerianates, should be folded first in waxed paper and then each covered with tinfoil and dispensed in a bottle.

4. **Powders in quantity.**—When a powder is ordered to be given in spoonfuls, it should be dispensed in a well-corked or stoppered wide-mouthed bottle.

5. **Salts** which mutually decompose each other must be mixed and stirred lightly together in a dry condition ; as sodium sulphate with potassium tartrate, potassium nitrate with sodium salicylate.

6. **Oxidising substances** should be each separately rubbed to powder, and then lightly blended on paper with safe ingredients by a bone spatula.

7. **Hygroscopic powdered drugs** should never be kept in paper packets. They should be dried and preserved in wide-mouthed bottles or stone jars with accurately fitted stoppers or corks. Suspending a bag of dry quicklime from the cork helps also to keep powders dry.

8. **Division of powders.**—There should be no guess work in division. **Each one must be weighed.**

9. **Liquids** are rarely prescribed in powders ; if so, white kieselguhr may be used to absorb them (1 gr. to 1 m.).

CAPSULES AND CACHETS

Capsules are used in place of pills to dispense nauseous and disagreeable drugs. Solids, semi-solids and liquids in small bulk may be dispensed in capsules. They are made of gelatin with varying quantities of glycerin depending upon the hardness required. They are of two varieties, soft and flexible, usually oval in shape for liquid and semi-soft, masses ; and hard for dispensing powders. They readily become soft, dissolve in the stomach and are taken like pills.

The hard capsules consist of a body and a cap, the latter fitting over the other like a lid. They are filled with a small aluminium funnel and the powder is pressed through it with a thin glass rod or a stick. The cap or lid is moistened on the inner side with a camel-hair brush and pushed home on the other half to which it adheres.

Soft capsules are oval in shape with a long closed neck. The filling of these capsules requires some practice. The neck is cut off and the measured quantity of liquid is introduced by means of a hypodermic syringe and the open end sealed either by melting the cut-end with a hot glass rod or a steel spatula ; or by placing on the cut-end a little melted glyco-gelatin.

When capsules are intended to act in the intestine without being dissolved in the stomach, they should be coated with a solution of keratin or immersed in a solution of formaldehyde, B.P. for ten minutes. They are then known as enteric coated or 'glutoid' capsules.

Cachet forms an excellent medium of prescribing nauseous and bitter powders, of larger amount than can be supplied in a capsule. They are made of wafer paper so that they become soft and pulpy when moistened with water and these can be easily swallowed without tasting the drug. They are made of two kinds, one 'wet seal' and the other 'dry seal.'

The dry closing cachets consist of two halves one fitting over

the other like hard gelatin capsules. These are very easy to fill. The required quantity of the drug is placed in one half and the other half of the lid is placed on it.

The wet seal cachets consist of two halves with a broad rim. The powder is deposited in one half, the margin of the other half is moistened with water and placed over the other and the rims pressed together. These are best filled by wet-closing Cachet Machine.

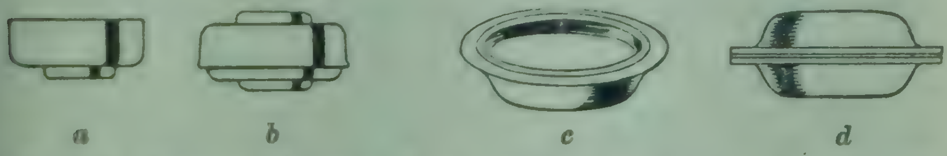


Fig. 42.—Cachets showing "dry seal" (*a* and *b*), and "wet seal" (*c* and *d*) open and closed.

The machine consists of three plates joined by hinges (fig. 43). The plates have two or more sets of holes so that different sizes of cachets may be used in the same machine. The plates being open, one half of the cachet is placed in the hole in plate A and the other half into the corresponding hole in plate C. The plate A is now covered with plate B and the empty cachets are filled with the required quantity of powder through the funnel D with the help of

Fig. 43.—Cachet Machine.

thimble E. The middle plate is now removed and the rims of the empty cachets on plate C are damped with the roller moistened with water and the plate turned over and lightly pressed on plate A so that two halves of the cachets get fixed. The finished cachets are then removed and served in boxes.

BLISTERS

1. **Blister Spreading.**—A blister is best spread over an adhesive plaster, which has been previously spread upon glazed thin calico.

First of all the dispenser should cut a "shape" an exact size and form of the blister ordered—out of square piece of writing or packing paper, leaving all round a margin 1 inch wide. This is best done by folding the square piece twice upon itself, and cutting by a pair of scissors the shape of the blister out of the middle, rejecting the cut out central piece. The *empty space is the shape of the blister.* The dispenser now cuts a piece of spread adhesive plaster or adhesive plaster mull one inch bigger than the size ordered, and gently warms it to make it slightly sticky, and quickly lays the "shape" upon its sticky surface, and evenly presses it down (in India the warming of the adhesive plaster is not often necessary during hot months). He then takes a quantity of the cantharidin plaster sufficient for the size and softens it well between his thumb and fingers. Taking a small pellet, he spreads over the adhesive surface, with the side and front of his right thumb, while the fingers of his left hand keeps the plaster *in situ.* He goes on making a series of rainbow-like strokes from left to right till the whole of the surface within the shape is covered. A long spatula is gently warmed and firmly passed over the spread cantharidin, removing any superfluous plaster and making its surface smooth. The paper shape is now removed, and the edges are trimmed, keeping a margin of the plaster three-eighths of an inch wide. A piece of oiled or waxed paper is now loosely laid over the blister and the whole put within a paper box.

Paper-covering should be removed before use, otherwise the blister will not stick. Both the dispenser and prescriber should give directions to this effect. A better plan is to pin the margins to a piece of paper which is then stuck to the bottom of the box.

PLASTERS

Most of the plaster-mulls of the market are made by machinery. Dispensing of such a spread plaster means the cutting of a piece ordered. It is only when a special plaster is ordered that the dispenser is required to make one on the counter. The spreading of a plaster requires great skill and dexterity.

1. **Plaster spreading.**—A plaster is made in the same manner as a blister, except that the method of spreading is different. Sheepskin, stiff chamois, dimity, moleskin or sometimes adhesive plaster-mull is used, but the white sheepskin is generally preferred when not otherwise ordered by the prescriber. The "shape" is cut in the same way as for a blister. A piece of leather larger than the size of the plaster ordered, is cut off and stretched out in all directions by pulling. The leather is now placed with its rough surface upwards on a thick pad of paper, and the gently warmed plaster iron is passed over it to remove any wrinkles or inequalities. The paper shape merely dipped in water is evenly pressed against this rough surface, and all the necessary appliances being in readiness the process of spreading is done in one of the following ways :—

(*a*) The plaster is cut into thin slices, put in a small enamelled pan with a lip and handle, and warmed over a gas flame or fire, stirring it constantly and not allowing it to boil. In the meantime the leather, the shape, and the plaster iron or spatula are kept ready as already described. As soon as the plaster becomes creamy, it is poured over the leather within the shape at the left end, then with a long spatula or a plaster iron it is spread rapidly over the surface, any superfluous plaster being removed and returned to the pot.

(*b*) The easiest and most convenient method of spreading is to cut a piece of plaster from the stick, allowing 15 grs. for each square inch of plaster required, and to put it on a sheet of strong, smooth, brown paper. Having prepared the shape and the leather,

melt the cut-off piece to a creamy consistence by gentle rubbing a hot plaster iron over it, and scrape the mass to the edge of the paper. The leather with the shape, having been brought alongside with one or two sweeps the dispenser covers the whole surface, removing any superfluous plaster with a spatula. A second hot iron may be required at this stage.

A mixture of plasters can be made by a similar process.

2. **Plaster with an adhesive margin** is made in the following manner :—The shape is cut as before, and the central piece instead of being thrown away, is damped and stuck to the middle of the leather. The shape is again folded up, and a piece of the width of the intended adhesive margin is cut off ; and the shape is pressed against the leather, thus leaving a free space between the centre piece and the shape ; which space is now covered over with the adhesive plaster. When cold, remove both the papers and apply a second shape cut to the proper size, having previously coated it lightly with soft soap to prevent it from sticking to the adhesive margin. The plaster is now spread in the ordinary way, the shape removed, and any soap that may have adhered to the margin is wiped away with a wet cloth or sponge.

3. **Plasters for bed-sores** are spread on chamois leather without margins.

4. **Mammary plasters** must be circular in shape, 7-in. diameter, with an opening 2-in. in diameter in the centre. The margin is to be notched to fit these plasters to the curved surface of the breasts.

SUPPOSITORIES, PESSARIES AND BOUGIES

1. **Basis.**—Oil of theobroma is the official basis. It should be liquefied on a water-bath in a casserole or a porcelain evaporating dish. In India where the prevailing temperatures are higher than in England, a sufficiency of white beeswax may be added to raise the melting-point to the necessary degree. An alternative method is to use *glyco-gelatin basis*, which consists of gelatin 25 ; glycerin 40 (by wt.) ; and water 80 (by wt.). This should only be used when ordered, since gelatin is incompatible with several substances including tannin.

2. **Ingredients** should be treated like those for ointments. Any powder or crystalline substance must be rubbed very fine with a little cacao butter, before mixing with the melted oil of theobroma.

3. **Moulds** are necessary to make suppositories. They are made of heavy gun-metal with six to twelve holes into which the melted suppository mass is poured. The mould is divided longitudinally so that it can be opened and cleaned. Each half of the mould contains the corresponding hollows, which when fixed and screwed form the entire suppository holes. They are so made that each hole has the capacity of holding a 15 gr. suppository.

Moulds must be perfectly clean and cooled with ice or cold water and the inner surface of the hollows lubricated with a piece of cotton wool soaked in a solution of soft soap and glycerin, each 1 part and alcohol (90 p.c.) 5 parts.

4. **Operation.**—Triturate as in para 2, and mix with the melted oil of theobroma with constant stirring, until a creamy mass without lumps is obtained, and then pour it into the moulds, or divide into equal parts when hard, and mould them with the fingers into the shapes of suppositories, pessaries and bougies. Finely powdered starch prevents them from sticking during manipulation.

5. **Capacity and Displacement.**—Ordinarily a mould will hold 15 gr. of oil of theobroma, but may hold more or less, depending on the density of the drug used. The quantity of the medicament which will displace one part of cacao butter is known as the *displacement value*. This requires to be taken into consideration when

calculating the amount of oil of theobroma necessary for each suppository. Thus 0.9 gr. of tannic acid and 3.6 gr. of iodoform will displace 1 gr. of oil of theobroma.

SUPPOSITORIES AND BOUGIES OF SPECIAL DRUGS

1. **Adrenaline** should be dissolved in about 10 minims of 1 in 30 boric acid solution and then mixed with suppository basis which consists of a mixture of oil of theobroma and sodium stearate 1/2 gr. for each suppository ordered. Stir till an emulsion is formed and pour into the mould when about to set.

2. **Alkaloids.**—Alkaloidal salts are generally better absorbed than pure alkaloids, and therefore the salts instead of the alkaloids should be used dissolved in oleic acid.

3. **Boric Acid** makes a good mass if glycerinum acidi borici and gelatin basis are mixed together.

4. **Chloral Hydrate** should not be mixed with heated cacao butter, but rubbed up with cold cacao butter and a little wax, if necessary, and pressed into the mould.

5. **Extracts** must be made into a smooth paste with water or proof spirit, and gradually mixed with the melted basis.

6. **Ichthammol** suppositories are made with glyco-gelatin basis when each suppository is more than 2 grs., otherwise oil of theobroma may be used. The ichthammol should be added directly to the melted oil of theobroma.

7. **Iodoform** makes good bougies and suppositories with cacao butter by the cold process. The crystals must be finely powdered in a glass mortar before being incorporated in the oil.

Despatching.—Suppositories should be sent out wrapped in absorbent cotton-wool. In hot weather, they may be dispensed in a wide-mouthed stoppered bottle containing iced water. If they contain volatile ingredients, each of them should be covered with waxed paper or tinfoil.

TINCTURES

In the preparation of tinctures three things are essential, *viz.*—(1) the **Solvent** ; (2) the **Process** ; and (3) the **Ingredients.**

1. **Solvent.**—Alcohol of various strengths is used in the preparation of most tinctures. One only, *viz.*, Tinct. Lobeliae Aetherea is prepared with ether. Ammonia is used in the preparation of Tinct. Valerianae Ammoniata. Glycerin and distilled water are used to help solution of active ingredients.

2. **Process.**—Any of the following processes is used for making tinctures :—

(*a*) *Maceration.*—Place the solid materials with the whole of the menstruum in a closed vessel ; shake occasionally during seven days ; strain ; press the marc, mix the strained and expressed fluids ; filter. It takes seven days and is not economical.

(*b*) *Percolation.*—Moisten the solid materials with sufficient menstruum, set aside for 4 hours in a well-closed vessel ; pack in a percolator, add sufficient menstruum to saturate the material. When the liquid drips from the percolator close the outlet, add sufficient menstruum to leave a layer above the drug. Macerate for 24 hours. Allow to proceed till the percolate measures about three fourth of the volume required for the finished tincture. Press the marc, mix the expressed liquid with the percolate, add sufficient menstruum to produce the required volume, filter.

(*c*) *Simple Solution.*—This method is adopted when tinctures are made by dilution of a liquid extract or a stronger tincture.

3. **Ingredients.**—These require to be carefully selected. Most of them are to be *powdered* according to the degree of comminution

as prescribed by the B. P. Some are to be *cut small*, some to be *bruised* and some are used in their natural state.

LOZENGES

1. **The B.P. lozenges** are made like a pill-mass (*see* page 36).

2. **Ingredients.**—The essential ingredients for making lozenges are finely powdered or icing sugar, mucilage of picked gum acacia, and medicinal and flavouring agents.

3. **Operation.**—The ingredients having been thoroughly mixed and kneaded, the resulting paste is placed on a slab with adjustable edges and rolled out to the desired thickness. The lozenges are then cut out with a punch and exposed to the air, 12 or 24 hours, after which they are removed to a drying chamber.

4. **Stamping.**—While the lozenges are still soft, they are stamped with letters indicative of their composition.

5. **Packing.**—Lozenges should be kept in dry, well-fitted stoppered bottles in a dry place. Dampness makes them sticky. They are to be dispensed in wide-mouthed stoppered bottles.

OINTMENTS

1. **The preparation of ointments** is not always easy. Special tact and care can only turn out a good product. The following **general hints are worth remembering :—**

(*a*) If the active drug is a *solid* or a *powder*, it should be reduced to a state of fine powder before admixture with the basis. so that the ointment may be free from grittiness.

(*b*) If it is *soluble* or *deliquescent salt*, as potassium carbonate or iodide, it should be first made into a thin paste with water before **mixing with the basis.**

(*c*) If it is a *hard extract*, a *balsam*, or a *resin*, a preliminary treatment is necessary with such substances as water, oil, glycerin, **or rectified spirit, as the case may be.**

(*d*) If it is a *liquid extract*, as in the case of belladonna ointment, it must be evaporated to the required consistence.

(*e*) If it is an *alkaloid*, as aconitine, atropine or cocaine, it should be dissolved in oleic acid by trituration and gentle heat.

(*f*) If it is a *crystallised drug*, as boric acid, salicylic acid, iodoform, etc., it should be reduced to a fine powder, and triturated with its own weight of the basis for a while before adding the rest. Tannic acid should first be dissolved in glycerin.

(*g*) If it is a *volatile substance*, such as menthol, chloral hydrate, it should be mixed after all the ingredients have been incorporated so as to reduce its evaporation to minimum.

2. **Basis.**—Ointments are used either for protection or for the emmolient effect, or as vehicle for various solid or liquid medicaments. When used for the former purpose they consist of mixtures of solid or liquid hydrocarbons, fats, animal or vegetable oils, waxes, higher alcohols and soaps. Water may be incorporated either in the form of a water-in oil or an oil-in-water dispersion. As has been pointed out (page 745) greasy ointment bases have certain disadvantages and have been replaced by "water soluble" or "washable" ointment bases. These contain 50 to 70 p.c. of water and some of the following, *viz.*, paraffin, liquid paraffin, cetyl alcohol, stearyl alcohol, glycerin and sodium lauryl sulphate. Emulsifying wax (Lanette Wax) introduced as an ingredient of "washable" basis contains cetostearyl alcohol and sodium lauryl sulphate. Ointment of wool alcohols (Eucerin Anhydrous) also serves as a washable ointment base. These are specially used for the preparation of **Penicillin Cream and Penicillin Ointment.**

Whatever basis is selected it should not be a chemical incompatible, nor should it in any way affect the action of the ointment.

Rancid lard or ointment should not be used. If the basis becomes too soft on account of the prevailing high temperatures, as in India, benzoinated lard, lard, or beeswax may be added as required.

When the basis contains substances like hard paraffin, beeswax, lead plaster or such ingredients which are solid at the ordinary temperature, and have to be incorporated with soft paraffin, lard, suet or an oily substance, it is necessary that they should be prepared by fusion, *i.e.*, by melting them in a porcelain dish on a water bath. The substances with a high melting point should be shredded and melted first and the other ingredients of the base added according to their melting point.

3. **Incorporation of liquid** with a fatty or oily basis is best effected by slowly adding the liquid drop by drop, and keeping up a steady rotatory motion. The mortar must be warmed beforehand.

4. **Spatulas.**—A bone or boxwood spatula is the best for scraping, stirring or mixing ointments.

5. Two ointments, or an ointment and a liquid or oily substances, are best mixed on a porcelain slab.

6. **Oleates** should not be melted in a metallic cup, but in a porcelain casserole.

7. **Tinctures and spirituous substances** are best incorporated with a fatty medium by spreading the latter evenly on the bottom and side of a mortar, and mixing the tinctures gradually.

Despatching.—Ointments should be sent out in earthenware pots with celluloid caps, a piece of waxed paper intervening between the cover and the ointment. They may also be sent out in glass jars having glass or aluminium covers. Collapsible tubes are convenient for small quantities and when the ointment is made by fusion. When open pots are used a tinfoil should be used over the waxed paper.

OINTMENTS OF SPECIAL DRUGS

1. **Unguentum Phenolis, B.P.** is best prepared by using liquefied phenol and a cold basis, as a previously prepared part of the phenol crystallises on keeping. This is obviated by dissolving the phenol in glycerin.

2. **Chrysarobinum** being more soluble in castor oil than lard, a mixture of the two gives satisfactory result.

3. **Glycerin** can be well incorporated with extracts by first rubbing the extract with a little hot water in a warm mortar and then adding glycerin gradually.

4. **Hydrargyri Perchloridum** is sometimes prescribed in the form of ointment. It must be well triturated with glycerin (2 ms. to 1 gr.) before mixing with basis, otherwise minute particles of it may violently irritate the skin. When ordered with potassium iodide, each should be triturated first before admixture.

5. **Iodide.**—First triturate, then add a few drops of rectified spirit and rub with its own weight of fatty basis, and lastly mix with the remaining basis.

6. **Paraffin ointment, B.P.**—Unless the melted paraffins are stirred well, the ointment is sure to be lumpy. White soft paraffin should be used for colourless ointments.

7. **Resorcin** readily absorbs oxygen and becomes discoloured.

8. **Thymol crystals** are very irritating to the skin. With camphor (1 in 1), thymol forms a liquid which can be worked up into an ointment.

9. Eye **ointments** or **oculenta** must be prepared under aseptic conditions according to the directions given in the B.P. Suitable glass rods for the application of the ointment should be supplied and their use explained to the patient.

PENICILLIN PREPARATIONS

General Consideration

Since dispensing of penicillin in different forms presents new problem, it is necessary that it should be discussed separately. The dispenser should be familiar with the following properties of penicillin :

1. Penicillin undergoes hydrolysis with loss of activity in the presence of moisture.
2. It is inactivated by acids and alkalies. The pH for optimum stability is 6.0.
3. The rates of hydrolytic deterioration increases with rise of temperature. Therefore all penicillin preparations should be kept at as low a temperature as possible.
4. It is rapidly deteriorated or inactivated in contact with alcohol, heavy metals, oxidizing agents.
5. Quite a large number of bacteria, including some air bacteria produce in an aqueous media an enzyme, penicillinase, which destroys penicillin.

Therefore any of the above substances must not come in contact with penicillin.

Bacteriological cleanliness.—This is important but it does not follow that all preparations containing penicillin should be sterile. Ointments and creams intended for infected wounds must be free from any contamination so that they may not convey an additional infection for the body defences to destroy. But ointments intended for superficial application or even to small cuts or wounds need not be free from the non-pathogenic organisms normally found on the intact skin. Since the oral cavity is not sterile, lozenges or pastilles need not be sterilised. Similarly there is no necessity of observing aseptic precautions for preparations of snuffs. But sterility is essential in the preparations which favour the growth of bacteria and steps should be taken to prevent growth of penicillinase-producing organisms specially in the preparations containing moisture.

Aseptic dispensing.—This is more important with regard to different injections. Since all injections are finally to be sterilised by autoclaving, absolute sterility during the different stages of preparation is not essential though desirable. It is very important that after incorporation of penicillin no heat should be applied. It is implied however that the other ingredients should be sterilised first and penicillin added in such a way that no extraneous contamination can occur.

Mixtures.—Penicillin is sometimes used in a mixture. One that has been used successfully contains at least part of it as an adsorbate in combination with aluminium hydroxide gel. First dissolve penicillin in water, add aluminium hydroxide gel in small quantities at a time ; shake after each addition, mix well and add water to the required volume.

Injections

Injectio Penicillini, B.P.—In this the solvent (sterilised by autoclaving) is simply added to the vial containing the penicillin. It is better to use some sterile ampoules containing the solvent. This injection will remain potent for 7 days at room temperature, though B. P. requires temperature not exceeding 4°C.

Injectio Penicillini Oleosa, B.P.—It contains beeswax and arachis oil. These should first be sterilised by heating at 150° for one hour and then filter through coarse filter paper. Cool. Triturate penicillin with a small quantity of the base in a sterile mortar to form a smooth paste first and then slowly add the remainder of the base. Distribute in sterilised containers and seal.

Ethyl oleate is used in place of arachis oil as this remains in a more fluid condition and does not require to be warmed before use.

Capsules

These are made either with sodium salt or calcium salt. Sodium salt is simply transferred to a gelatin capsule, sealed and enclosed in a larger capsule and immersed in a 1 in 20 dilution of 40 p.c. formaldehyde solution for 5 seconds first and then in alcohol (95 p.c.) for 5 minutes.

Calcium salt is generally incorporated with a fatty basis like wool fat and neutral and sterile olive oil. First melt the wool fat in the olive oil and allow to cool. Triturate penicillin in the mixture in a sterile mortar with aseptic precautions. Fill the resulting suspension into capsules with a hypodermic syringe. Seal and harden as before with formaldehyde and alcohol.

Dusting Powders

These are used for application to wounds and therefore they require to be prepared with aseptic precautions. The diluent may be lactose, or sulphonamides.

1. **Lactose** is first dried at 110° to 120°C. and then sterilised by heating at 150°C. for an hour, this may make it yellowish in colour. Penicillin is mixed with lactose in a sterilised mortar.

2. **Sulphathiazole** or **sulphanilamide** is often prescribed with penicillin. First remove any moisture by heating the sulphonamide at 100°C. and then spread it in thin layer in the hot air oven and heat for an hour at 150°C. After cooling add gradually calcium penicillin in a sterile mortar. Finally sift through a sterile No. 200 sieve.

Ointments and Creams

Since these are used for a wide variety of purposes sterilisation is not always necessary, but depends upon the purpose for which the cream or ointment has to be employed. When however these are to be used for packing wounds they must be sterile and should not contain any antiseptic. The object of sterilising the cream is primarily to ensure that penicillinase-producing organisms cannot exist and thus destroy the activity of penicillin. This result can however be achieved more easily and with greater security by adding some antiseptic like chlorocresol.

Cremor Penicillini, B. P.—Dissolve chlorocresol with gentle heat in distilled water. Cool to about 60°C. Melt together with gentle heat, the emulsifying wax, hard paraffin and liquid paraffin. Transfer to a suitable container and cool to about 60°C. Dissolve penicillin in chlorocresol solution and add it to the warm basis in the container, close, shake vigorously for a few minutes and cool rapidly.

Besides the bases recommended in the B. P., other bases for preparing Penicillin Cream or Ointment are in use.

1. Cetyl alcohol base consists of

Methylparaben		1½ gr.
Sod. Lauryl Sulph.		20 grs.
Cetyl alcohol		165 grs.
Arachis Oil		375 grs.
Aq. Destil.	ad	3½ oz.

Methylparaben is methyl-*p*-aminobenzoate. It is less toxic than either salicylic acid or benzoic acid. It is used as a preventive against growth of mould and forms an ingredient of Hydrophylic Ointment, U.S.P. which forms a basis for oil-in-water type of ointment and is readily removable from the skin and clothing. It should not be used for eye ointment.

2. Another ointment base for making penicillin ointment is

Emulsifying wax	300 grs.
Paraffin Liq.	2 oz.
Aq. Dest.	4½ oz.

N.B.—In place of liquid paraffin white soft paraffin 750 grs. may be used.

STERILISATION

The use of different preparations which are introduced into the body through different channels and of other preparations like the ointments for the eye, demands that these should be sterile, *i.e.* free from living micro-organisms. A knowledge of the various methods of sterilisation is therefore necessary. The methods generally adopted for the purpose involve either application of heat (moist or dry), filtration, use of certain chemicals, or a combination of these. Whatever method may be adopted it must be such as will not inactivate the medicament, or render the preparation subjected to the process, unsuitable for the purpose for which it is specially intended.

Since heat kills most bacteria, sterilisation by heat is generally the most suitable and convenient method. It is therefore the method of choice for thermostable substances, while filtration is adopted for thermolabile substances. Certain chemicals have a marked disinfectant action and kill most bacteria. But it is necessary to mention that some of these substances are used as a preservative in sterile solution as a precaution against possible reinfection. The chemicals generally used are phenol, cresol, chlorocresol, and chlorbutol. Sodium chloride increases the potency of phenol and cresol as antiseptic.

The Pharmacopoeia sanctions the following methods for sterilisation :—

1. Sterilisation of Glass Vessels and Containers

Glass vessels and containers are well freed from grease and are then sterilised by heating at a temperature not lower than 150° for one hour, or by exposing to saturated steam in an autoclave at 115° to 116° for thirty minutes.

2. Sterilisation by Heating in an Autoclave

A solution or preparation to be sterilised by heating in an autoclave is distributed in suitable containers, which are then finally sealed. When the volume in each container does not exceed 100 millilitres, the containers are exposed to saturated steam at 115° to 116° for thirty minutes. When the volume in each container exceeds 100 millilitres, the containers are exposed for a longer time, sufficient to ensure that the whole of the solution in each container is maintained at the temperature of 115° to 116° for thirty minutes.

3. Sterilisation by Heating with a Bactericide

The solution is prepared by dissolving or suspending the medicament in a 0.2 p.c. w/v solution of chlorocresol in Water for Injection or in a 0.002 p.c. w/v solution of Phenylmercuric Nitrate in Water for Injection. The solution or suspension of medicament is distributed in the final containers, which are then finally sealed. When the volume in each container does not exceed 30 millilitres the containers are heated at 98° to 100° for thirty minutes. When the volume exceeds 30 millilitres, the containers are heated for a longer time, sufficient to ensure that the whole of the solution or preparation in each container is maintained at the temperature of 98° to 100° for thirty minutes.

Solutions of medicaments to be used for intravenous injection shall not be prepared by this method when a single dose of the injection is greater than 15 millilitres.

Solutions of medicaments to be used for intrathecal or intracisternal injection shall not be prepared by this method.

4. Sterilisation by Filtration

A solution to be sterilised by filtration is filtered through a sterile bacteria-proof filter. After the solution has been distributed with aseptic technique into the final sterilised containers, and these have been sealed, the solution is submitted to the *Tests for Sterility,* and must comply with these tests.

5. Sterilisation of Oily Solutions and Suspensions

A solution or suspension in oil is distributed in the final containers, which are then either finally sealed, or temporarily closed so as to exclude bacteria. When the volume in each container does not exceed 30 millilitres, the containers are heated at 150° for one hour. When the volume in each container exceeds 30 millilitres, the containers are heated for a longer time sufficient to ensure that the whole of the solution or suspension in each container is maintained at 150° for one hour. Containers which have been temporarily closed are then finally sealed. When the solution or suspension cannot be submitted to this temperature without the production of physical or chemical change, the solution or suspension is prepared by aseptic methods, and oil or Ethyl Oleate, which has previously been heated at 150° for one hour, is used. The solution or suspension is transferred to previously sterilised containers, and these are sealed so as to exclude bacteria.

6. Dispensing of Parenteral Injections

Containers.—Solutions or preparations of drugs to be administered by parenteral injection or the sterile medicaments to be used for the preparation of such solutions are dispensed in single-dose or multiple-dose containers sealed so as to exclude bacteria.

Solutions intended for intrathecal, intracisternal or peridural injection are dispensed only in single-dose containers.

Multiple-dose containers.—When the container is sealed so as to permit the withdrawal of successive doses on different occasions, the solution or preparation of the drug contains a suitable bacteriostatic agent in such a concentration as will prevent the growth of micro-organisms.

Rubber caps used for closing such containers are made from a good quality heat-vulcanised rubber. They are boiled in several changes of *water* and then either boiled under a reflux condenser for thirty minutes, or stored for not less than forty-eight hours, in a solution containing the same bacteriostatic agent, and in the same concentration, as that used in preparing the injection.

NOTE.—In any emergency in which the methods described above or any special method described in a monograph cannot be applied, it is the duty of the dispenser to inform the prescriber that complete sterilisation cannot be attempted, and to obtain the prescriber's approval for the method to be adopted.

APPENDIX I

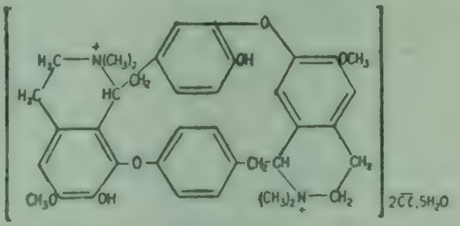
ADDENDUM 1951 TO THE

BRITISH PHARMACOPOEIA, 1948

New Additions

Aethinyloestradiol.—See page 449.
Benzylpenicillinum.—See page 568.
Cetrimidum.—See page 725.
Chloramphenicol.—See page 584.
Dicophanum. Syn.—D.D.T.—See page 733.
Dihydrostreptomycinum.—See page 580
Dimercaprol. Syn.—B.A.L. British Anti-Lewisite.—See page 532
Indicarminum. Syn.—Sodium Indigotindisulphonate.—See page 422.
Mepyraminae Maleas.—See page 437.
Oxophenarsinae Hydrochloridum.—See page 524.
Oxophenarsinae Tartras.—See page 525.
Pheniodol.—See page 384.
Phenolsulphonphthaleinum. Syn.—Phenol Red.—See page 423.
Procainae Benzylpenicillinum. Syn.—Procaine Penicillin G.—See page 568.
Proguanili Hydrochloridum. Syn.—Paludrine.—See page 495.
Promethazinae Hydrochloridum. Syn.—Phenergan.—See page 437.
Propylthiouracil.—See page 633.
Streptomycini et Calcii Chloridum.—See page 579.
Streptomycini Hydrochloridum.—See page 579.
Streptomycini Sulphas.—See page 580.
Sulphadimidina.—See page 550.
Sulphadimidina Sodium.—See page 551.
Vanillinum.—See page 753.

Tubocurarinae Chloridum.—*d*-Tubocurarine Chloride is the chloride of an alkaloid, *d*-tubocurarine, obtained from the stems of plants of the genus *Chondrodendron*, and possessing the specific biological activity of curare on neuromuscular transmission. See page 261.



Characters.—A white microcrystalline powder; odourless. Sparingly soluble in water and in alcohol (95 p.c.); more soluble in warm water and solutions of alkali hydroxides.

B. P. Dose.—To be determined by the physician in accordance with the needs of the patient.

Sodii Citras Acidus. Syn.—Disodium Hydrogen Citrate.—Sodium Acid Citrate may be preapred by the interaction of citric acid and sodium carbonate.

Characters.—A white powder; odourless; taste, saline. Soluble in less than 2 parts of water; insoluble in alcohol (90 p.c.)

Action and Uses.—It is an anticoagulant and is largely used with dextrose for transfusion (page 678). It has the advantage over sodium citrate in that the solution can be sterilised in an autoclave with little caramelisation. Moreover when added to blood it prolongs its preservative action.

Isoprenalinae Sulphas.—Isoprenaline Sulphate is 1-(3 : 4-dihydroxyphenyl)-3-*iso*propylaminoethanol sulphate. Contains 5.3 to 5.5 p.c. of N, and 6.0 to 6.3 p.c. S. See page 319.

Characters.—A colourless, crystalline powder ; odourless. Soluble in about 4 parts of water : almost insoluble in alcohol (95 p.c.), in chloroform and solvent ether.

B. P. Dose.—1/6 to 1/2 gr. or 10 to 30 mg.

Methacholinae Chloridum.—Methacholine Chloride is acetyl-methyl-choline hydrochloride. See page 237.

Characters.—Colourless or white crystals, or a white crystalline powder ; odourless or with a slight odour. Very deliquescent. Very soluble in water : freely soluble in alcohol (95 p.c.) and in chloroform.

B. P. Dose.—1½ to 3 gr. or 0.1 to 0.2 grm. *By hypodermic Injection* **: 1/6 to 2/5 gr. or 10 to 25 mg.**

Quinalbarbitonum Sodium. Syn.—Seconal Sodium.—Quinalbarbitone Sodium is the mono-sodium derivative of 5-allyl-5 (1-methylbutyl) barbituric acid. See page 211.

Characters.—A white powder ; odourless ; taste, bitter. Hygroscopic. Very soluble in water : soluble in alcohol (95 p.c.) : practically insoluble in solvent ether.

B. P. Dose.—3/4 to 3 gr. or 50 to 200 mg.

Monographs on Preparations of **Human Blood, see page, 676.**

APPENDIX II

CONTRACTION OF WORDS AND PHRASES USED IN PRESCRIPTIONS

The following contractions of words are ordinarily used in prescriptions :—

Contr.	*Name*	*Meaning*
Aa	Ana	Of each
Ad.	Adde	Add
Amplus	..	Large
Aq.	Aqua	Water
Aut	..	Or
C.	Cum	With
Cap., Cpt.	Capiat	Let the patient take
Cibus	..	Food
Co. or Comp.	Compositus	Compound
Cum	..	With
Cyath.	Cyathus	A glass
Div.	Divide	Divide
Et.	..	And
F.	Fac	Make
Ft.	Fiat	Let it be made
Garg.	Gargarisma	A gargle
Gr.	Granum	A grain
Gtt.	Gutta	A drop
Haust.	Haustus	A draught
H.	Hora	An hour
In	..	In or into
Ind.	Indies	Daily
Levis	..	Light
M.	Massa	A mass
M.	Misce	Mix
M. or Min.	Minimum	A Minim
Mag.	Magnus	Large
Mane	..	In the morning
Mist.	Mistura	A mixture
Mitte	..	Send
Mol.	Mollis	Soft
Nox.	..	Night
Om.	Omnis	All, every
Post	..	After
R.	Recipe	Take
Rept.	Repetatur	Let it be repeated
Sig.	Signetur	Let it be labeled
Sine	..	Without
Ss.	Semis	Half
Somnus	..	Sleep
Stat.	Statim	Immediately
Sum.	Sume	Take
Talis	..	Such
Una	..	Together
Vel.	..	Or
Ver.	Verus	Genuine
Vesp.	Vesper	The evening
Vetus	..	Old
Vitellus	..	The yolk of an egg.

The following contractions of phrases are often used in prescriptions :—

Contraction	*Phrase*	*Meaning*
Ad lib.	Ad libitum	At pleasure.
A. H.	Alternis Horis	Every other hour.
A. C.	Anti cibus	Before food.
Aq. Bull.	Aqua Bulliens	Boiling water.
„ Dest.	„ Destillata	Distilled water.
„ Ferv.	„ Fervens	Hot water.
„ Font.	„ Fontalis	Spring water.
„ Pluv.	„ Pluvialis	Rain water.
Bis. ind. or B.D.	Bis indies	Twice daily.
C.m.	Cras mane	To-morrow morning.
C.n.	Cras nocte	To-morrow night.
Coch. amp.	Cochleare amplum	A table-spoonful.
„ mag.	„ magnum	Do.
„ mod	„ modicum	A dessert-spoonful.

Contraction	*Phrase*	*Meaning*
Coch. min. ..	.. Cochleare minimum	.. A small spoonful or a tea-spoonful.
„ parv. ..	.. „ parvum	.. A tea-spoonful.
C. Vin. ..	.. Cyathus Vinarius	.. A wine-glass.
Dieb. alt. ..	.. Diebus alternis	.. On alternate days.
D. in p. æ or Div. in p. æq.	.. Dividatur in partes .. aequales ..	.. Let it be divided into equal .. parts.
Ft. Haust. ..	.. Fiat Haustus ..	.. Let a draught be made.
F. M. or Ft. Mist.	.. Fiat Mistura ..	.. Let a mixture be made.
H. D. ..	.. Hora decubitus	.. At bedtime.
H. S. or H. S. S.	.. Hora Somni Sumendum	.. To be taken at bed time.
M. B. ..	.. Misce Bene ..	.. Mix well.
M. D. U. ..	.. More dicto utendum	.. To be used as directed.
M. P. ..	.. Massa Pilularis	.. A pill mass.
O. h. ..	.. Omni hora ..	.. Every hour.
O. m. ..	.. Omni mane ..	.. Every morning.
Omn. bih. ..	.. Omni bihora ..	.. Every two hours.
O. n. ..	.. Omni nocte ..	.. Every night.
P. C. ..	.. Post Cibus ..	.. After food.
P. R. N. ..	.. Pro re nata ..	.. When required, occasionally.
Q. S. ..	.. Quantum sufficiat	.. Sufficient quantity.
Q. H. ..	.. Quaque hora ..	.. Each hour.
S. O. S. ..	. Si opus sit ..	.. If necessary.
S. S. ..	. Statim sumendum	.. Immediately to be taken.
T. d. ..	. Ter in die ..	.. Thrice daily.

APPENDIX III

ALTERNATIVE PREPARATIONS SANCTIONED FOR USE IN TROPICAL, SUBTROPICAL, AND OTHER PARTS OF THE BRITISH EMPIRE

Aurantii Cortex.—In parts of the Empire where bitter oranges cannot be obtained, either dried bitter-orange peel or fresh sweet orange peel may be used in preparing tincture of orange.

Extracta Liquida.—Any Pharmacopoeial liquid extract containing less than 30 p. c. v/v of ethyl alcohol, may have the proportion increased to an amount not exceeding 30 p. c. v/v, where otherwise the preparation will be liable to ferment.

Limonis Cortex Siccatus.—When fresh lemon peel cannot be obtained, dried lemon peel may be used in preparing fresh and concentrated compound infusions of gentian, syrup of lemon, and tincture of lemon.

Unguenta.—Varying quantities of lard, yellow beeswax, or white beeswax, wool fat, hard paraffin, soft paraffin or liquid paraffin, may be employed in the preparation of the ointments of the Pharmacopoeia when prevailing high temperatures otherwise render the basis too soft for convenient use ; but the official proportion of the active ingredient must in all cases be maintained.

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